Evaluating User Perceptions and Experiences of Dual Compartment Microbicide Formulations: *Developing Rectal USPE Measures for Suppositories (Project DRUM-S)*

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Principal Investigator:	Robert W Buckheit, Jr, PhD ImQuest Pharmaceuticals, Inc. 7340 Executive Way Suite R Frederick, Maryland 21704 Phone: 301.696.0274; Fax: 301.696.0381 E-mail: rbuckheit@imquestbio.com
Project Leader:	Kate Guthrie, PhD (née Kathleen Morrow) Centers for Behavioral & Preventive Medicine The Miriam Hospital / Brown Medical School Coro West, Suite 309 1 Hoppin Street Providence, Rhode Island 02903 Office: 401.793.8180; Fax: 401.793.8165 Email: kate.guthrie@lifespan.org
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LIST OF ACRONYMS

AE:	Adverse Event
AIDS:	Acquired Immune Deficiency Syndrome
CASI:	Computer-Assisted Self-Interview
CDC:	Centers for Disease Control and Prevention
DAERS:	DAIDS Adverse Experience Reporting System
DAIDS:	Division of AIDS
DAIDS MO:	DAIDS Medical Officer
DAIDS PRO:	DAIDS Protocol Registration Office
DAIDS RCC:	DAIDS Regulatory Compliance Center
EAE:	Expedited Adverse Event
FDA:	Food and Drug Administration
GRAS:	Generally Recognized As Safe
HEC:	Hydroxyethyl cellulose (HEC gel)
HIPAA:	Health Insurance Portability and Accountability Act
IBD:	Inflammatory Bowel Disease
ICF:	Informed Consent Form (written)
IDI:	In-Depth Interview (for DRUM-S, with Cognitive Interview Elements, as necessary)
IoR:	Investigator of Record
IPCP:	Integrated Preclinical/Clinical Program (U19)
IRB:	Institutional Review Board: human subjects protection, ethics board
MIP:	Microbicide Innovation Program
MOP:	Manual of Operational Procedures
MSM:	Men who have Sex with Men
N9:	Nonoxynol-9
NIAID:	National Institutes of Allergies and Infectious Diseases
NIH:	National Institutes of Health
OTC:	Over-the-Counter
PI:	Principal Investigator
PSRT:	Protocol Safety Review Team
QA:	Quality Assurance
QC:	Quality Control

QPTC:	Qualified Professional Test Counselor (RIDOH certification for HIV counseling/testing)
RAI:	Receptive Anal Intercourse
RIN:	Research Identification Number
RSC:	Regulatory Support Center
RIDOH:	Rhode Island Department of Health
RIN:	Research Identification Number
RPR:	Rapid Plasma Reagin (screening test for syphilis)
SAE:	Serious Adverse Event
STI:	Sexually Transmitted Infection
SUSAR:	Suspected, Unexpected Serious Adverse Reactions
TMH:	The Miriam Hospital: subcontract institution and performance site
U19:	Grant mechanism of this protocol
USPE:	User Sensory Perceptions and Experiences
UTI:	Urinary Tract Infection
WSM:	Women who have Sex with Men

PROTOCOL SUMMARY

Study Purpose	To adapt existing user sensory perception and experience (USPE) items/instruments generated for rectal gel/cream formulations to include USPEs specific to suppository forms for rectal and vaginal use. For both male and female cohorts: to capture the experience of suppository use in the context of receptive anal intercourse (RAI). For female cohort only: to capture the experience of suppository use in the context of vaginal-penile intercourse (VI), and to compare USPEs of suppository use in the context of RAI to USPEs of suppository use in the context of vaginal-penile intercourse.
Study Design	Single-site, pre-phase 1, mixed methods USPE instrument development study
Study Population	Healthy, HIV uninfected participants, male ≥18 years of age and female 18-45 years of age. By history receptive anal intercourse (RAI) at least twice in the past 6 months and women in addition vaginal-penile intercourse (VI) at least twice in the past 6 months.
Sample Size	Approximately 20-30 participants (~10-15 males; ~10-15 females). Our goal is to recruit a minimum of ~7-10 males and ~7-10 females. Ranges are provided to allow for a gender imbalance in the sample if we experience difficultly with recruitment, and to allow for achieving data saturation in qualitative data collection.
Study Contacts	Visit 0: Pre-screening (by phone or in person) to confirm basic eligibility Visit 1: Informed consent (Screening), STI/HIV screening; pregnancy screening (females); CASI Clinic Survey Visit 2: Pregnancy screening (females), informed consent (Formulation Evaluation), random assignment to order of study products, provision of 1st study product, CASI Baseline Survey Visits 3-4: Pregnancy screening (females), provision of 2nd and 3rd study products, respectively Visit 5: In-depth qualitative interview (IDI) with survey evaluation (cognitive) elements Visit 2-Visit 5: Automated daily phone check-ins Web-based USPE surveys completed following each occurrence of RAI/VI in conjunction with study product use. Final product acceptability survey completed after the final USPE survey. Compensation for all study activities completed since the previous visit (daily phone check-ins, web-based surveys) and not yet compensated, will occur with each study visit
Study Duration	Study duration: Participant recruitment, enrollment, visit completions: 9-12 months. Analyses: within 24 months from start of study. Per participant: Approximately 10-20 weeks. We do not anticipate the necessity of additional time beyond the range allotted for female participants to evaluate suppositories in both compartments (§3).
Study Regimen/ Intervention	Products : -- HEC gel (CONRAD, Arlington, VA) – applicator insertion -- Key-E suppository –manual insertion -- Zetpil suppository – manual insertion

Primary Objectives	1) Adapt existing USPE items for evaluation of suppository-associated user sensory perceptions and experiences within the context of rectal or dual compartment use, and 2) Using 2 distinct suppository formulations and 1 gel formulation that represent a range of rheological and other biophysical properties of potential microbicides being designed for rectal/dual compartment use, evaluate the experience of suppository use (as compared to gel use) in the context of receptive anal intercourse among males and females, and in the context of vaginal intercourse (females).
Primary Endpoint **Exploratory Endpoints**	1. Generate adapted and novel rectal USPE items to be used in evaluating the perceptibility, user experience and acceptability of rectal and dual compartment topical formulations, as proposed in the parent grant. 2. Characterize USPEs of gel and suppository formulations used for RAI and VI using both existing and novel USPE items/scales. 3. Collect participant-reported information regarding the safety of the suppository forms. The information collected will include any adverse events (and their severity grading) deemed to be related to the suppository dosage form by the study clinical staff and/or in consultation with the DAIDS Medical Officer. 4. Identify formulation-specific classes of USPE scale scores (Sex-associated scales): by sex (males, females), by compartment (rectum (males, females); vagina (females)), resulting from Latent Class modeling analyses, given adequate final evaluable sample sizes.
Participating Site	The Miriam Hospital, Providence RI, USA

Key Roles and Contact Information

Kate Guthrie, PhD (née Kathleen Morrow) Investigator of Record and Co-Investigator Centers for Behavioral & Preventive Medicine The Miriam Hospital and Brown Medical School Coro West, Suite 309 1 Hoppin Street Providence RI 02903 Phone: 401.793.8180 / Fax: 401.793.8165 Email: kate.guthrie@lifespan.org	**Joseph L Fava, PhD** Co-Investigator, Psychometrician/Statistician Centers for Behavioral & Preventive Medicine The Miriam Hospital Coro East, 1st floor 1 Hoppin Street Providence RI 02903 Phone: 401.793.8025 / Fax: 401.793.8078 Email: jfava@lifespan.org
Erna (Milu) Kojic, MD Study Clinician Immunology Center The Miriam Hospital and Brown Medical School 1125 North Main Street, Rm 249 Providence, RI 02906 Phone: 401.793.5961 Fax: 401.793.4779 / Pager: 401.350.2788 E-mail: ekojic@lifespan.org	**Kelley Alison Smith, MPH** Project Director Centers for Behavioral & Preventive Medicine The Miriam Hospital Coro West, Suite 309 1 Hoppin Street Providence RI 02903 Phone: 401.793.8364 / Fax: 401.793.8165 Email: ksmith20@lifespan.org
Sheila Tumilty, RN Clinical Trial Nurse Immunology Center The Miriam Hospital 1125 North Main Street, Rm 233 Providence, RI 02906 Phone: 401.793.2126 / Fax: 401.793.4779 E-mail: stumilty@lifespan.org	**Rochelle Rosen, PhD** Research Scientist Centers for Behavioral & Preventive Medicine The Miriam Hospital and Brown University SPH Coro West, Suite 309 1 Hoppin Street Providence RI 02903 Phone: 401.793.8182 / Fax: 401.793.8165 Email: rrosen@lifespan.org
Melissa Guillen Research Assistant Centers for Behavioral & Preventive Medicine The Miriam Hospital Coro West, Suite 309 1 Hoppin Street Providence RI 02903 Phone: 401.793.8143 / Fax: 401.793.8165 Email: mguillen@lifespan.org	**Melissa L. Getz** Research Assistant Centers for Behavioral & Preventive Medicine The Miriam Hospital Coro West, Suite 309 1 Hoppin Street Providence RI 02903 Phone: 401.793.8123 / Fax: 401.793.8165 Email: mgetz@lifespan.org
Sara Vargas, PhD Post-doctoral Research Fellow Centers for Behavioral & Preventive Medicine The Miriam Hospital and Brown Medical School Coro West, Suite 309 1 Hoppin Street Providence RI 02903 Phone: 401.793.8014 / Fax: 401.793.8165 Email: svargas@lifespan.org	**Candelaria Barroso** Senior Research Specialist Centers for Behavioral & Preventive Medicine The Miriam Hospital Coro West, Suite 309 1 Hoppin Street Providence RI 02903 Phone: 401.793.8066 / Fax: 401.793.8165 Email: cbarroso@lifespan.org

Bruce Barton, BS & Renee Fraatz, Pharm. D., R.Ph. Investigational Pharmacy Services The Miriam Hospital 164 Summit Ave Providence, RI 02906 Phone: 401.793.7646 / Fax: 401.793.3043	**Anthony Ham, PhD,** Co-Investigator ImQuest BioSciences, Inc. 7340 Executive Way, Suite R Frederick, Maryland 21704 Phone: 301.696.0274 / Fax: 301.696.0381 E-mail: aham@imquestbio.com
David Katz, PhD, Co-Investigator Duke University Box 90281 Durham, NC 27708 Phone: 919.660.5452 E-mail: dkatz@duke.edu	**Craig Hendrix, MD,** Co-Investigator Director, Drug Development Unit Division of Clinical Pharmacology The Johns Hopkins Hospital 600 North Wolfe Street, Harvey 502 Baltimore, MD 21287-5554 USA Phone: 410.955.9707 / Fax: 410.955.9708 Email: cwhendrix@jhmi.edu
Robert W Buckheit, Jr, PhD Principal Investigator ImQuest BioSciences, Inc. 7340 Executive Way, Suite R Frederick, Maryland 21704 Phone: 301.696.0274 / Fax: 301.696.0381 E-mail: rbuckheit@imquestbio.com	**Karen M Buckheit** Director, Topical Microbicide Research ImQuest BioSciences, Inc. 7340 Executive Way, Suite R Frederick, MD 21704 Phone: 301.696.0274 / Fax: 301.696.0381 E-mail: kbuckheit@imquestbio.com
Jim A Turpin, PhD Preclinical Microbicides & Prevention Research Branch (PMPRB), Prevention Sciences Program DAIDS, NIAID, NIH 5601 Fishers Lane; Room 8B31 Rockville, MD 20852 Phone: (301) 451-2732 / Fax: (240) 627-3465 Email: jturpin@niaid.nih.gov	**Hans ML Spiegel, MD, Contractor** Medical Officer, PMPRB/Prevention Sciences Program DAIDS, NIAID, NIH 5601 Fishers Lane; Room 8B51A Rockville, MD 20852 Tel: 240-292-4633 / Fax: 240-627-3465 Email: hans.spiegel@nih.gov
Cherlynn Mathias, RN, BSN Program Officer/Nurse Consultant Prevention Science Program DAIDS, NIAID, NIH 5601 Fishers Lane; Room 8B51B Rockville, MD 20852 Tel: 240-292-4791 / Fax: 240-627-3465 E-Mail: cmathias@niaid.nih.gov	

1. Introduction

1.1 Overall Study Rationale

1.1.1. Acceptability, Adherence, and Perceptibility in Microbicide Product Development

HIV prevention is a global public health priority. Despite advances in the development of vaginal microbicide gels, effectiveness trials to date have been challenged by poor user adherence.[1-3]– Post-hoc analyses from the CAPRISA-004 tenofovir gel study,[4] as well as those from the VOICE and FACTS trials, show that participants who reported better adherence rates experienced a greater reduction in HIV infections than those who reported average adherence. These analyses suggest that in order to develop products that have the greatest likelihood of use, more end-user research on the barriers and facilitators of product use is needed.[5]

Current conceptualizations of adherence and acceptability have failed to recognize that patterns of use and non-use during clinical trials may be related in part to how a product feels to users and impacts the sexual experience. A formulation's properties affect both drug delivery and how a user perceives it. Microbicide developers therefore have the opportunity to develop products that can achieve performance standards for both behavioral and biological functions. Understanding which formulation properties distinguish important user experiences (i.e., perceptibility) is critical to creating products that can be targeted to specific end-users based on preferences for sensory experiences.

To this point, we have developed and validated perceptibility measures to better understand user sensory perceptions and experiences (USPEs) with topical gel products (i.e., semi-solid gels and film formulations). Perceptibility evaluation emphasizes the correspondence between physicochemical/rheological performance of formulations and how users sense and perceive those characteristics and behaviors, and can also capture the correspondence between the user experience and willingness-to-use.[6] By evaluating perceptibility of formulation properties and performance characteristics early in the development process, we hope to identify those that are clearly not amenable to continued development, and begin to understand which user experiences may promote both acceptability and adherence.

Developers are now beginning to investigate whether suppositories may be an acceptable formulation for dual compartment use.[7-9] In Project DRUM (parent award U19 AI101961), we adapted and integrated USPE measures into the preclinical science of developing a dual compartment, anti-HIV microbicide. The study, DRUM-S (U19 AI101961), will incorporate perceptibility science into the development of a dual-compartment anti-HIV microbicide in suppository form and to compare those data with existing and newly acquired USPEs of a known gel formulation (HEC).

Developing validated USPE measures for suppository formulations will allow investigators to broaden the concept of perceptibility and capture a greater range of sexual experiences in the context of topical HIV prevention formulations. By incorporating the user experience early in the product development process, developers will have the greatest chance of providing at-risk individuals with the best possible prevention methods. Prevention products that can be used in either (or both) the rectum and the vagina - and that optimize the user experience - are more likely to be used consistently and correctly. The impact on global public health has the potential to be far-reaching, decreasing HIV and STI incidence in both women and men.

1.1.2 Formative Work in User Sensory Perception and Experience (USPE)

Previous Research in Vaginal Formulation Perceptibility. Dr. Guthrie's (née Morrow) research team has, over the past 15 years, conducted acceptability studies for four vaginal microbicide clinical trials (HIVNET009, HPTN020, HPTN049, HPTN050)[10-12] and generated several psychometrically validated scales of contextual factors hypothesized to be related to a woman's willingness to use a vaginal gel microbicide (R01MH064455).[13-18] Most recently the team has been evaluating qualitative and quantitative data to advance the field's understanding of the correspondence between sensory perceptions of product behavior in the vagina, and properties of vaginal gels/films designed for coital use.[19,20] The current protocol builds upon existing work in a preclinical framework (R21/R33MH80591 & PPA-09-023 CONRAD, PI: Guthrie (née Morrow); U19AI077289 (PI: Buckheit); R33AI076967 (PI: Buckheit)).

Dr. Guthrie's Microbicide Innovation Program award (R21/R33MH80591), known as Project LINK, developed ~20 perceptibility scales measuring USPEs of gel behavior, and identified an additional 139 individual items whose mean product ratings alone show statistically significant differences between the products evaluated. Our findings[20] suggest that users can perceive differences between topical vaginal gels with different biophysical and rheological properties, and that the differences in sensations and experiences are associated with their choice of gel for an HIV prevention product. A secondary analyses of Project LINK results, using latent class modeling, identified patterns of scale scores that characterize user experiences across the coital episode.[6] These analyses suggested that the overall patterns of experience suggest a rational approach to formulation design, and that by extension, 1) users of a certain formulation may report, as a function of their USPE scale scores, somewhat varied patterns of experience, and 2) users may have specific sensory experiences that outweigh more global evaluations of product experience. For example, the results suggest that sensations of smoothness and lubricity during initial penile penetration are critical to a user's evaluation of that product.[21,22]

In subsequent work (Project MIST: R33AI076967: Buckheit, PI), the role of volume in USPEs has been evaluated, using a single gel delivering two different volumes, as well as a quick-dissolving vaginal film. In this study, couples were enrolled and the sexual activity perceptibility scales were adapted in order to capture actual intercourse and both male and female partners' USPEs. Psychometric analyses suggest that the scales are robust and continue to capture the targeted USPEs. Perceptibility scale scores show that USPEs of specific formulations are rated similarly across sex. Importantly for formulation development, they show clear distinctions between the two gel volume conditions and between each of the gel and film formulations. In addition, one of the critical results from Project MIST was the identification of six (6) additional perceptibility scales associated with the sexual experience, accounting for added volume of the formulation and a quick-dissolving film with significantly different rheological and other biophysical properties. These additional USPE scales underscore the need to continue to expand the evaluable parameters of topical formulations, so that products under development, including potential suppository formulations, can be rationally designed for acceptability and adherence.

The Current IPCP's Progress in Rectal and Dual Compartment Perceptibility. Investigators in the current IPCP have been pioneering perceptibility research on vaginal gels and films; namely, joint analysis of how product properties govern both USPEs and drug delivery. Project 5 investigators, and other investigators under the parent award (U19 AI101961), have developed and validated the first set of perceptibility measures for topical vaginal gels and films,[23-25] and have adapted these measures for rectal gel formulations (Project DRUM and Project 4). Within the context of the parent award's overall aim, the current study will continue formative research to identify and characterize the range of USPEs in the context of receptive anal intercourse (RAI) and vaginal intercourse (VI), using three formulations applied in the rectum (males and females) and in the vagina (females). Most importantly, two of these will be suppository forms. The suppository formulation (1) has yet to be evaluated from a perceptibility

perspective, and (2) is considered to be the likely dual compartment drug delivery formulation to move forward in this IPCP award.

Project DRUM (Project 5.1, U19 AI101961) was the first time perceptibility science was incorporated in the process of developing a dual compartment, anti-HIV microbicide. Vaginal USPE scales were adapted for rectal formulation evaluation of 3 different gel products. The gels varied across multiple rheological traits, including viscosity. For some items, wording was directly changed from "vagina/vaginal" to "rectum/rectal" (or "anus/anal canal/anal"), particularly when specifying location of product insertion or location of the sensory experience. In other instances, items were generated from rectal-specific experiences described in the literature, such as sensations of gas/bloat, or bowel sensations that did not apply to vaginal USPEs. Despite the relatively low sample size (N=15), the overall psychometric properties of the subscales and their items were very good. The scales also performed well in Project 4 (which assessed volume in the rectal compartment (Johns Hopkins Univ. (Hendrix)), using these newly adapted rectal USPE items to evaluate USPE scale scores as a function of formulation volume.) data. Twenty scales captured insertion, ambulation, and sexual USPEs: 5 evaluated sensations experienced during product insertion, 1 evaluated sensations experienced during ambulation post-product insertion (if applicable), and 14 evaluated sensations experienced during receptive anal intercourse (RAI)**.** While initial psychometrics for the scales adapted from vaginal to rectal compartments are encouraging, a much larger sample size would be required to fully validate the measures for rectal USPEs. The current study will contribute additional data to that effort.

Nearly all of the 20 scales had very good to excellent psychometric properties for both averaged loadings and Cronbach's alpha values for all three gels. Effect size differences between gels in the overall sample (N=15) were generally in the small to medium range. There were smaller effects when comparing gels with the combined sample (males and females combined), and greater within and between sex differences, indicating that there was some differential reporting of experiences between the sexes. In general, females had higher reported mean item level subscale scores than males, and the majority of the higher differences occurred within the RAI USPE subscales.

While largely a formative study, the consistently good preliminary psychometrics for the adapted rectal USPE items provide evidence that these sensory experiences can be objectively measured, that they maintain quality of measurement in a novel web-based data collection environment, and that they may contribute to our understanding of the RAI experience as potentially unique in males versus females. As we continue to accrue the necessary data to conduct more thorough psychometric studies, we also seek to continue to develop our understanding of the role that sensory experience plays in users' decision-making with respect to other potential rectal and vaginal formulations for HIV prevention.

1.1.3. Project DRUM-S

DRUM-S (Project 5.3, U19 AI101961), proposed here, will be the first to incorporate perceptibility science into the development of a dual-compartment anti-HIV microbicide in <u>suppository</u> form and to compare those data with USPEs of a referent gel formulation (HEC). It will also be the first to examine <u>vaginal</u> delivery of suppository forms, given the goal of a dual compartment product. The three formulations to be used in this study (HEC gel, and Key-E®and Zetpil® suppositories; see §1.3) were chosen because of the range of physicochemical and rheological properties they exhibit.

We have opted to include the HEC gel arm because of the psychometric nature of the study. HEC gel has been the one soft material form included in each USPE scale development study. It bridges the data between studies and allows the psychometric data to build in credibility (in essence, providing a <u>constant</u> for standardization).

The suppositories have properties both similar to and different from suppository forms being considered by the Formulation Core (Dr. Ham) for evaluation as dual compartment microbicides (e.g., the hardness of the suppository for insertion; size and shape of the suppository; dissolution time), all of which have implications for how the formulations feel to users. Because the properties of the Key-E suppository, in particular, have been instrumental in the development of the parent U19 suppository formulation, both the USPE scale scores and the in-depth qualitative data captured in the current study will provide important feedback to the Formulation Core.

Having USPE scale scores from evaluations in different compartments (vaginal v. rectal), in different volumes in the same compartment (4 mL v. 10 mL), and in comparison to other formulations with markedly different rheological and biophysical properties (gel v. film v. suppository) will allow us to confirm hypotheses regarding how product properties, volumes, and vaginal/rectal geography impact sensations elicited during use. Once validated, these measures will be available to be used in subsequent clinical trials of the dual compartment microbicide being developed in the parent award.

1.1.4 Study Significance

Achieving significant gains in the prevention of sexually-acquired HIV presents a particular challenge to global public health efforts. Risk reduction is often less of a concern in a sexual encounter than is a satisfactory sexual experience. Thus, to ensure that methods intended for HIV prevention achieve targeted public health outcomes, they should be developed to meet users' needs and wants. Too often, however, product development occurs apart from full consideration of the user perspective, yielding products that challenge adherence within the context of clinical trials and/or to maintenance of use in the real-world context. We anticipate that correct and consistent use of prevention products would improve if products both optimize users' preferred use experience and effectively address HIV prevention.

The current study will extend this work, increasing the parameter space of topical formulations for use in the rectum, by moving beyond gels (as in DRUM) with varying rheological and other biophysical properties, to include suppository forms. In addition, the current protocol will, for the first time, also evaluate USPEs of suppository formulations in the context of vaginal sex. Evaluations will consist of user ratings of sensory perceptions and experiences (USPEs) within the context of receptive anal intercourse (RAI), in cohorts of men who have sex with men (MSM) and women who have sex with men (WSM), as well as USPEs within the context of vaginal-penile intercourse for WSM.

1.2 Study Goals

The primary goals of Project DRUM-S are to:

1) Adapt existing USPE items for evaluation of suppository-associated user sensory perceptions and experiences within the context of rectal, vaginal, and/or dual compartment use, and

2) Using 2 distinct suppository formulations and 1 gel formulation that represent a range of rheological and other biophysical properties of potential microbicides being designed for rectal/dual compartment use, evaluate the experience of suppository use (as compared to gel use) in the context of receptive anal intercourse among males and females, and in the context of vaginal intercourse (females).

Quantitative data will be collected via phone, web, and CASI surveys. Demographic data will allow description and characterization of the study sample, as well as stratifications and/or covariates other than formulations for potential analyses. Survey data will result in user ratings of relevant constructs within the users' sensory perceptions and experiences.

Qualitative data will provide an opportunity to identify any remaining conceptual gaps in formulation-specific USPE evaluation, or in perceptibility phenomena, as a function of specific compartment (rectum,

vagina) or sexual behavior sequencing, as well as identify any issues in current USPE item adaptations. This will occur via a relatively brief semi-structured qualitative interview.

Given the formative nature of this stage of study, standard hypothesis testing is not an appropriate endpoint. Initial characterization of the sensory experiences of female and male users, via both the quantitative scale scores and the narrative qualitative data, and development of rectal-specific, vaginal-specific, and dual compartment USPE measures with respect to suppository forms are the primary goals.

1.3 Study Products

1.3.1 Description of Study Product Formulation and Preparation

No product used in this study will include anti-HIV compounds/drugs.

HEC Gel

HEC gel will be obtained from CONRAD and shipped to The Miriam Hospital Pharmacy Department. HEC gel will be shipped in single-dose pre-filled HTI Comfort Tip applicators, each in its own sealed pouch, appropriately labelled as per regulatory guidelines.

HEC gel was developed as a placebo for microbicide clinical trials. All ingredients used in the manufacture of the HEC gel are compendial (United States Pharmacopeia/ National Formulary) and are considered safe for use in topical pharmaceutical preparations. Hydroxyethyl cellulose is used as the gel thickener. HEC gel was made isotonic to reduce the risk of epithelial damage caused by cell swelling or dehydration. The formulation was also made slightly acidic (pH 4.4). Buffering capacity, however, is minimal. Sorbic acid was selected as a preservative based on its safety profile and lack of activity against HIV *in vitro*. The HEC gel does not contain any active pharmaceutical ingredient. (See Investigator's Brochure for further details.)

HEC Gel: Components	**Percentage (w/w)**
Purified Water, USP	96.3
Hydroxyethyl Cellulose, NF (Natrosol 250 HX Pharm)	2.7
Sodium Chloride, USP	0.85
Sorbic Acid, NF	0.1
Sodium Hydroxide	qs pH 4.4

The FDA's inactive ingredients list (FDA Inactive Ingredients Database (http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm), lists Hydroxyethyl cellulose (HEC) as a gel formulation for topical applications. However, the FDA inactive ingredients list does not specifically list vaginal or rectal use. Although the vaginal or rectal route of administration is not specifically identified in the FDA database, HEC has been developed and used in the formulation of a universal placebo gel, as a baseline comparison in microbicide development in clinical trials.[26] As a result, HEC has been used in several vaginal formulations and studies, most notably in the 1% TFV gel used in the CAPRISA 004, VOICE, and FACTS-001 trials.[4,27] For rectal microbicides HEC-based gels have been investigated as well.[28,29]. All the remaining ingredients used in this formulation are listed as excipients in both vaginal and rectal products.

The Miriam Hospital Pharmacy Department will package the study product, two 4mL prefilled HTI Comfort Tip applicators, and gauze, in labeled resealable light-blocking amber pharmacy bags. The label will be the designated study product color (i.e., orange) and will also contain text noting the color coded product.

Key-E® Suppositories

Key-E suppositories are available over-the-counter and approved for both rectal and vaginal use. Ingredients, inclusive, are listed as Natural-source Vitamin E (30 IU), and the base is hydrogenated coconut oil and palm oil. The suppository dissolves in approximately 15 minutes and does not require refrigeration (they are stored at room temperature but can be refrigerated to increase hardness if preferred). Recommended dosing is one suppository, one or more times per day, and is indicated "to ease discomfort and to lubricate areas with extreme dryness." (CarlsonLabs.com)

Key-E® suppositories will be obtained from the distributor and shipped to The Miriam Hospital Pharmacy Department. Two (2) doses of study product per evaluation, in their original per dose packaging, will be packaged in labeled resealable light-blocking amber pharmacy bags. The label will be the designated study product color (i.e., yellow) and will also contain text noting the color coded product.

Zetpil® Suppositories

Zetpil® suppositories are available over-the-counter for both rectal and vaginal use. Ingredients include vitamin B1 (3 mg), vitamin B2 (3 mg), vitamin B3/Niacinamide (10 mg), vitamin B6 (5 mg), pantothenic acid (10 mg), vitamin B7 (0.4 mg), Vitamin B12 (0.8 mg), folinic acid (1 mg), calcium (150 mg), L-Dopa from mucuna puriens, theanine, theobromine, N-Acetyl cysteine, Huperzine A 1%, vinpocetine/vincamine derivative (from the periwinkle plant), phosphatidylcholine, phosphatidylserine (Proprietary blend), and the base is plant/fruit butter, vegetable acids, triglycerides, phospholipids, lecithin, vegetable starches, cellulose, oligosaccharides, polysaccharides, and cycloamylose derivatives. The suppository dissolves in approximately 10 minutes and does not require refrigeration (they are stored at room temperature but can be refrigerated to increase hardness if preferred). Recommended dosing is one to two suppositories per day (not to exceed two).

Zetpil® suppositories will be obtained from the distributor and shipped to The Miriam Hospital Pharmacy Department. Two (2) doses of study product per evaluation, in their original per dose packaging, will be packaged in labeled resealable light-blocking amber pharmacy bags. The label will be the designated study product color (i.e., green) and will also contain text noting the color coded product.

1.3.2. Overview of Risks

Use of personal lubricants for anal intercourse is common among both men and women.[30] HEC gel has been used extensively in both vaginal [3,5,31] and, more recently, rectal microbicide studies.

As with all topical formulations, there is the possibility of allergies or sensitivities to the components in the study products (i.e., HEC gel, Key-E®, and Zetpil®). Both Key-E®, and Zetpil® can be administered more than once daily and there are no restrictions to sexual activity noted from the manufacturer. Additionally, a search of available literature found no published information regarding increased risk of side effects from using these products, either as indicated or during intercourse. Those study volunteers with known allergies to similar products or a history of irritation, inflammation, or other signs of sensitivity from similar products or ingredients will be excluded from the study.

All study products will be applied into the rectum (or vagina) using either the HTI Comfort Tip® applicator (gel) or via digital insertion (suppositories). Applicators have accounted for minor epithelial disruptions in vaginal microbicide trials, typically characterized as similar to speculum-related disruptions. For HEC gel, participants will be instructed to use a small amount of the study product to lubricate the applicator prior to insertion. Instructions for suppository use include a wait time of 15 minutes between product insertion and RAI/VI (see Appendix).

Staff will verbally review use of the applicator, showing each step using an empty demonstration applicator. At each product provision visit (V2-4) staff will instruct participants on appropriate insertion

of the assigned product. As part of this process, they will point out the detailed step-by-step instructions in written form. Participants will be given detailed written and illustrated instructions with each product to take home with them. This procedure has worked successfully in our previous vaginal and rectal product evaluation studies.

1.3.3 Pharmacy

All study products will be stored at the Miriam Hospital Pharmacy and dispensed following the receipt of a written prescription from the study clinician. The written prescription will be stored, as per regulatory guidelines, in the research pharmacy's study binder. The site pharmacist is required to maintain complete records of all study products received and subsequently dispensed. HEC will be destroyed per hospital policy after the study is completed or terminated. The two OTC products (Key-E® and Zetpil®) may be transferred to separate storage in Dr. Guthrie's lab, to be used for staff training and demonstration purposes only. The procedures to be followed are provided in *Requirements for Pharmacy Activities at DAIDS Supported Clinical Research Sites Conducting Trials Outside of the HIV/AIDS Clinical Trials Networks.*

2. Objectives

2.1 Primary Objectives

1) Adapt existing USPE items for evaluation of suppository-associated user sensory perceptions and experiences within the context of rectal or dual compartment use, and

2) Using 2 distinct suppository formulations and 1 gel formulation that represent a range of rheological and other biophysical properties of potential microbicides being designed for rectal/dual compartment use, evaluate the experience of suppository use (as compared to gel use) in the context of receptive anal intercourse among males and females, and, for females, in the context of vaginal intercourse.

2.1.1 Primary Endpoints

(1) Generate adapted and novel rectal USPE items to be used in evaluating the perceptibility, user experience and acceptability of rectal and dual compartment topical formulations. Items will be generated from qualitative interview data, thus narrative data (in the form of direct single-source quotes or aggregated quotes across participants with similar sensory and behavioral experiences) will be used to generate statements for subsequent scale items.

(2) Characterize USPEs of gel and suppository formulations used for RAI and VI using both existing and novel USPE items/scales. Averaged scale item scores for each USPE scale (5 application/insertion scales; 6 ambulation scales; 14 sexual activity scales) will be psychometrically evaluated and, further, will be used to conduct pair-wise comparisons and calculate the effect sizes associated with these comparisons (see section 8).

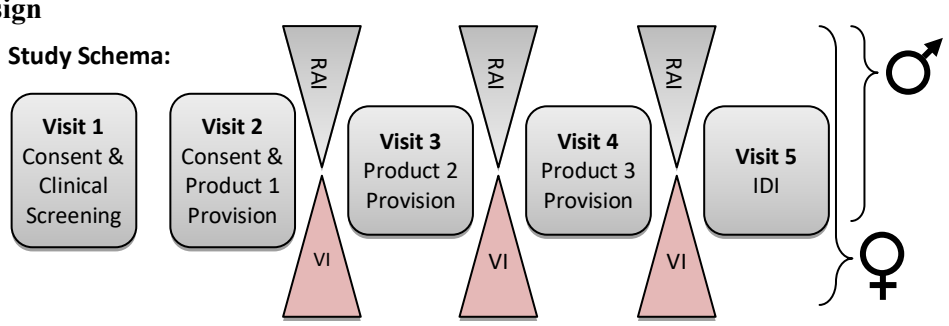
2.1.2 Exploratory Endpoints

(3) Collect participant-reported information regarding the safety of the suppository forms. The information collected will include any adverse events (and their severity grading) deemed to be related to the dosage form by the study clinical staff and/or in consultation with the DAIDS Medical Officer. Frequency of specific related adverse events (and their severity) will be calculated cumulatively.

(4) Identify formulation-specific classes of USPE scale scores (Sex-associated scales): by sex (males, females), by compartment (Rectum: males and females. Vagina: females), resulting from Latent Class modeling analyses, given adequate final evaluable sample sizes.

3. Study Design

Study Schema:



Visits occur at study clinic (V1) or behavioral lab (V2-V5). Product evaluation activities (RAI (receptive anal intercourse); VI (vaginal intercourse)) represented by triangles occur outside the clinic (e.g., participant's home). ALL participants complete study product evaluations with RAI. FEMALE participants also complete study product evaluations with VI.

This study is a single-site pre-Phase 1 USPE measure development study, utilizing a formative mixed-method design (i.e., incorporating qualitative and quantitative data collection methods). Approximately 20-30 participants (~10-15 males and ~10-15 females) will evaluate three products (Key-E®, Zetpil®, and HEC gel), on separate occasions, during RAI. In addition, female participants will evaluate the suppository products during vaginal sex. Participants will be assigned to one of six possible product orders.

Female participants are not required to have RAI and VI in the same sexual episode, or in different sexual episodes: we will allow them to choose, so that we can begin to understand how sexual sequencing may/may not play a role in product use for women. All participants will be instructed verbally and in writing to limit suppository use to a total of 2 per day, for the women, regardless of rectal or vaginal use.

Participant recruitment, enrollment, and visit completions will require approximately 9-12 months. Analyses (both quantitative and qualitative) will be complete within 24 months from study initiation. Results, in the form of USPE scale scores, by product, sex, and compartment, will be computed. Preliminary psychometric analyses of scales will be completed, given adequate evaluable sample size.

It is estimated that the time from initial prescreen through completion of the final visit for each participant will take, on average, 10-20 weeks. The maximum allowable time from STI/HIV/pregnancy screening to enrollment in the formulation evaluation study is 30 days. If more than 30 days pass and the participant still wishes to enroll in the study, s/he will be required to repeat the screening visit (V1). It is estimated that the prescreen (Visit 0), including, if eligible, collection of contact information, will take 15-25 minutes. Visits 1 and 2, including separate consenting processes, will take approximately 1-1.5 hours; Visits 3 and 4 will take <30 minutes; Visit 5, including the in-depth interview, will take approximately 1.5-2 hours. Daily phone check-ins will be brief (~3 minutes). Web-based USPE surveys will take approximately 45-90 minutes. As per our previous experience in Project DRUM, the average time between product provision visits is expected to be ~2 weeks. (See Appendix for Table of Visits and Study Activities)

4. Study Population

4.1 Selection of the Study Population

The study sample will consist of approximately 20-30 participants (~10-15 males and ~10-15 females) who engage in receptive anal intercourse (RAI; females must also engage in vaginal-penile intercourse,

(VI)). Based on samples previously recruited by this research team, the sample will likely consist of approximately 60-70% White/Caucasian and 30-40% non-White (e.g., Black/African American, Latina/Hispanic, American Indian/Alaska Native) individuals. As calculated from all volunteers who prescreened for Project DRUM and reported at least 1 RAI episode, females reported RAI an average of 14 times in the previous 6 months, with a range of 3-72; males reported RAI an average of 21 times in the previous 6 months, with a range of 4-50. As such, we are confident we will be able to recruit the volunteers necessary to meet the criteria below.

4.2 Inclusion Criteria

All participants must meet all of the inclusion criteria to participate in this study.

- Eligible male participants must be 18 years of age or older
- Eligible female participants must be 18-45 years of age
- Report receptive anal intercourse (RAI) at least twice in the past 6 months,
- Are willing to use each study product in conjunction with RAI on at least one occasion in each data collection period (resulting in a minimum of 3 RAI events during the study)
- Are willing and able to respond to study data collection systems via phone and internet, attend all study visits, and participate in in-depth qualitative interviews

Additional Inclusion Criteria for Female Volunteers:

- report vaginal-penile intercourse (VI) at least twice in the past 6 months,
- willing to use each study suppository formulation in conjunction with VI on at least one occasion in each data collection period (resulting in a minimum of 2 vaginal intercourse events during the course of the study)
- report consistent use of an effective birth control method: e.g., hormonal contraceptive, IUD, bilateral tubal ligation, Essure® or any non-incisional permanent birth control procedure, hysterectomy (partial or total, with/without oophorectomy), partner's vasectomy/salpingectomy

4.3 Exclusion Criteria

All potential participants meeting any of the exclusion criteria at screening or study visits will be excluded from study participation. Male and female participants will be ineligible if they:

- Have a sensitivity or allergy to vaginal, anal, or rectal products,
- Have a sensitivity or allergy to any of the ingredients contained in the study products
- Have a sensitivity or allergy to sesame seeds
- Are HIV-positive at baseline, or have a known HIV-positive sexual partner,
- Have an active rectal or reproductive tract infection requiring treatment per current CDC guidelines or have other condition that, in the opinion of the investigator/study clinician, make the patient unsuitable for the study or unable to comply with study requirements (Note: HSV seropositivity without active genital lesions is not an exclusion criteria).
- Urinary tract infection (UTI).
- Have current inflammatory bowel disease (IBD) or history of active IBD within last 3 months,
- Have any other significant colorectal symptom(s) as determined by medical history, participant self-report, or physical exam (including but not limited to presence of any unresolved injury, infectious or inflammatory condition of the local mucosa, presence of symptomatic external hemorrhoids, and presence of any painful anorectal conditions that would be tender to manipulation),

- Have any other clinical condition or prior therapy that, in the opinion of the investigator/study clinician, would make the patient unsuitable for the study or unable to comply with the study requirements (including, as determined by medical history, participant self-report, or physical exam),
- Are unwilling to refrain from use of nonoxynol-9 (N9) for the duration of the study
- Are currently enrolled in other rectal or vaginal product studies
- Are unable or unwilling to communicate in English, or
- Are unable or unwilling to give written informed consent

Additional Exclusion Criteria for Female Volunteers:

- Are pregnant or breastfeeding. Pregnancy testing will be conducted at Visits 1-4 (screening and prior to any product use period)
- Have completed menopause (i.e., at least 12 months without menstrual periods)
- Are currently attempting to get pregnant or have an intention to get pregnant during their participation in the study
- Are unwilling to refrain from use of any vaginal product (inclusive of douching; exclusive of tampons during menses) other than study products
- Have clinically significant abnormal pelvic findings and/or findings requiring therapy as a function of clinical exam at Visit 1
- Report being within 30 days of their last pregnancy outcome or gynecologic surgical procedure

** Note: In cases where GC/CT is identified at screening, one re-screening after documented treatment will be allowed if the study timeline permits.*

4.4 Prohibited Medications and Procedures

Study participants will be advised not to use the following throughout study participation: any rectally or vaginally administered products containing N9, sex toys (broadly defined) (tampons during menses are allowed), or any other rectal or vaginal investigational products.

If participants report using any of these products while enrolled in the study, their study product provision will be put on hold, pending discussions with study site investigator, Sponsor, and/or DAIDS MO. Study staff will have a list of prohibited medications/procedures that will be used when actively reviewing concomitant medication and non-medicated OTC vaginal/rectal product use with the research participants during screening and throughout conduct of the study.

4.5 Required Medications and Procedures

Condoms are recommended for use by participants enrolled in this study and will be strongly encouraged for all sexual encounters during the study period. Natural oils can reduce the integrity of latex condoms: since both suppositories contain natural oil(s), the study will provide non-latex condoms to participants in quantities expected to be sufficient for the study period. These condoms will not be impregnated or coated with any type of spermicide. In the event that a participant needs additional condoms between visits, s/he may request these from the study at any time.

5. Study Product Regimen

The products will be evaluated by male and female participants during receptive anal intercourse (see Section 6.3, Formulation Evaluation) and vaginal-penile intercourse (females only). No product used in this study will include any anti-HIV compounds or drugs. During each of three study periods (between visits 2 and 3, 3 and 4, and 4 and 5), participants will evaluate one formulation. Each formulation will be

evaluated by each participant, namely: HEC gel, Zetpil® suppository, and Key-E® suppository. The ordering of product presentation will be randomized (see section 6.2 below). Participants will be blind to formulation (each product will be assigned a color and will be referred to as such, (e.g., 'the orange product'; see §1.3.2). Study staff, including study clinicians and research staff, will not be blind to participant product assignments.

6. Study Procedures / Evaluation
See APPENDIX A: Schedule of Visits and Procedures

6.1 Overview

Volunteers will first enroll for STI/HIV/pregnancy screening and then, if eligible, for the Formulation Evaluation study activities. Once basic eligibility is determined (i.e., Visit 0, Prescreen; see section 6.1), potential participants will be scheduled for Visit 1 (See section 6.2 below). Name and other pertinent contact information (e.g., telephone number, address, email) for future confirmation or rescheduling of visit dates will be collected. At the first visit (Visit 1), staff will provide information about the visit, answer any questions, and obtain informed consent for those willing to participate in the screening process. Once consented, potential participants will be tested for STIs including HIV, and screened for any rectal signs or symptoms. Female participants will also be tested for pregnancy and screened for any vaginal signs or symptoms. If a participant meets the above eligibility criteria (with the exception of lab results) upon completion of Visit 1, and is still interested in participating, s/he will be tentatively scheduled for Visit 2, pending lab results. Once lab results are conveyed to the participant, and eligibility is confirmed, scheduling of Visit 2 will be confirmed. There is no minimum time requirement between V1 and V2. These visits will generally be scheduled approximately two weeks apart to allow for the processing and conveyance of lab results to the participant. If the participant does not enroll in Visit 2 within 30 days of completing Visit 1, s/he will be required to be re-screened (repeat V1) prior to Visit 2.

When an eligible and interested potential participant returns for Visit 2, staff will provide information about the remainder of the study, reconfirm eligibility (including a negative pregnancy test result for female participants), answer any remaining questions, and obtain informed consent. Once informed consent for the product evaluation portion of the study is obtained, the remainder of the study will proceed as detailed below (See section 6.3).

6.2 Recruitment and PreScreening (Visit 0)

Study volunteers will be recruited by methods common in the PI's research, including advertisements (e.g., posters and street outreach), recruitment sessions at clinics and community-based organizations and events, internet/intranet advertisements and electronic social networking strategies (e.g., Lifespan Intranet, Craigslist, Facebook, GRINDR), the research team's future studies contact list of previous participants who have given permission to be contacted for similar studies, and word-of-mouth from participants in various studies conducted by the PI and her colleagues. Initially, a volunteer will express interest in the study and, if necessary, provide her/his first name and telephone number and/or email for future contacts. Volunteers may contact staff by either calling the study phone number, emailing the study email account to arrange a time for prescreening, or completing the prescreener privately on location at a community-based site.

All interested volunteers will be assigned a Research Identification Number (RIN) as soon as contact with the study is initiated. Each RIN is only assigned once and never reused. Each volunteer will complete a brief prescreening questionnaire (Visit 0) administered verbally by study staff (either over the phone if interested individuals call in to the study office, or in person (and in private) if staff conduct recruitment activities at community organizations or events) (See APPENDIX: Questionnaire for Basic Eligibility: PreScreeners). Staff will read prescreening questions and potential responses aloud, and enter volunteers'

verbal responses into a secure prescreening computer database. Privacy during phone conversations will be established by the staff asking whether the volunteer is in a place where s/he can answer questions privately. Privacy for in-person prescreenings will be ensured by study staff having a quiet, private space arranged at the site. If volunteers feel at all uncomfortable with the privacy arrangements, staff will arrange for a phone prescreen to be conducted. Research staff will first describe study requirements and procedures, including risks, benefits, and compensation. Verbal consent for prescreening will be obtained prior to questioning. PreScreener questions have been piloted: administration times range between 15 and 25 minutes, with an average of 20 minutes per administration. If a volunteer meets all initial eligibility criteria s/he will be scheduled for Visit 1. No identifying information will be collected until the prescreening responses indicate initial eligibility (with the exception of first name and telephone number or email for rescheduling prescreening, if necessary). Once scheduled for V1, the volunteer's full name, address, and date of birth (necessary for clinic registration purposes), as well as contact information, will be collected in a separate file (not associated with the RIN-identified responses).

At any point in the prescreening process, an individual may choose to suspend the interaction for any reason. If this occurs, study staff will thank the individual for their time and interest and ask whether s/he would like to be included in a future studies contact log. The contact log is a password-protected database of individuals who are interested in our research and wish to be notified of future research opportunities. The information is not linked in any way back to a particular study. Only first name and preferred forms of contact (e.g., email or postal address, phone number) are maintained.

6.3 STI/HIV/Pregnancy Screening (Visit 1)

Once prescreening has been completed and a potential participant has met basic eligibility criteria, s/he will be scheduled for a clinical screening visit to be screened for STIs (N. gonorrhoeae, chlamydia trachomatis, and syphilis) and HIV (inclusive of pre- and post-test counseling), and (for female participants) pregnancy. Prior to any testing, staff will individually and privately provide information about the screening visit (Visit 1) and obtain informed consent. Participants will complete a brief CASI demographic survey.

A limited visual rectal exam will be performed on all volunteers (males and females) to screen for any rectal symptoms including lesions, chancroid, sores, ulcers, and warts. Laboratory specimens will be collected, including rectal swabs and urine for N. gonorrhoeae, trichomonas, and C. trachomatis by nucleic acid amplification, and serum for RPR testing to rule out syphilis. HIV testing will be done using a rapid HIV antibody test (e.g., OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test) that detects antibodies to HIV-1 and HIV-2 in 20 minutes. (See APPENDIX B: HIV Testing Algorithm)

For female volunteers, a limited visual pelvic exam will be performed to evaluate for any mucosal lesions or ulcers (external genital exam). Pelvic examinations may be deferred during menses. A pregnancy test will be done on a urine sample using a standard pregnancy test kit (e.g., QuPID® Plus, Stanbio Laboratories).

Risk behaviors will be assessed and appropriate risk reduction goals established during standard HIV/STI counseling and testing discussions with all participants. Procedures follow the Rhode Island Department of Health (RIDOH) guidelines. HIV counseling and testing will be done either by clinical staff, or by non-clinical research staff who have been certified by the RIDOH as Qualified Professional Test Counselors (i.e., hold initial QPTC certificates and are in good standing). A risk reduction plan may include referral to additional services, as well as behavioral risk reduction goals tailored to the specific risks of the individual. In addition, all those who enroll in the study agree to follow the study guidelines noted in the Inclusion/Exclusion criteria (see § 4.3/4.4). If a participant is unable to adhere to the study guidelines, s/he may be withdrawn from the study.

Should an individual receive a positive test result for a curable STI, that individual will first be informed of the result by the study clinician or designee. After the individual has been informed, the participant will be referred to their primary care physician for treatment. If they do not have a primary care physician, they will be referred to the study clinician for treatment, who will follow CDC Recommendations for the Treatment of STDs. Once successfully treated, the participant can be rescreened for eligibility if they so choose. If a female participant has a positive pregnancy test, she will be referred via the study's clinician to appropriate care of her own choice, inside or outside the Miriam Hospital/Lifespan network.

6.4 Formulation Evaluation (Visits 2-5)

6.4.1 Randomization to Product Presentation Order

Once a participant has been successfully screened for STI/HIV and pregnancy and remains interested in participating in the study, s/he will be scheduled for Visit 2 and assigned to a randomized product evaluation order. There are 6 such orderings: (1) HEC, Zetpil®, Key-E®; (2) HEC, Key-E®, Zetpil®; (3) Zetpil®, HEC, Key-E®; (4) Zetpil®, Key-E®, HEC; (5) Key-E®, HEC, Zetpil® (6) Key-E®, Zetpil®, HEC). Approximately 3-5 participants (~2 males and ~2 females) will be randomly assigned to each possible assignment order. If, for any reason, the participant does not enroll in the study after randomization, their assigned product order will be re-assigned to another participant.

6.4.2 CASI Survey

After completing the Visit 2 informed consent process, participants will complete a CASI survey collecting relevant information on their sexual and reproductive health history.

6.4.3 Product Demonstration

After completing the Visit 2 informed consent process, study staff will acquaint the participant with the study product that s/he has been assigned to evaluate at home during the first product evaluation period. Staff will verbally review the insertion instructions for the assigned product, as applicable; if the HEC gel, study staff will also demonstrate how to insert the gel into the applicator using a demonstration applicator. If a suppository product, staff will verbally review the insertion instructions for the assigned product. Additionally, study staff will provide a condom use demonstration, noting important knowledge (non-latex, expiry date) to be considered, as well as step-by-step instructions for opening the condom wrapper, removing the condom, applying it (using an artificial phallus for the demonstration), and discarding a used condom appropriately. Any questions regarding the product insertion process, and/or correct condom use will be answered.

6.4.4 Product Provision

Following the demonstration(s), study staff will review the study procedures and guidelines with the participant and then provide the participant with two (2) doses of their assigned study product, and written instructions for inserting the product and using the condoms: the 2nd dose is provided only as a back-up, in case the 1st dose is dropped or sex does not occur after product insertion. All participants (male and female) will be instructed to use the study product during RAI at least once during the product evaluation period (~2 weeks). Female participants will also be instructed to use a separate dose of the suppository products for VI. When suppository products are provided, participants will be instructed to wait 15 minutes before rectal or vaginal intercourse to allow for product dissolution. Participants will be strongly encouraged to use condoms throughout the duration of the study (§4.5).

6.5 Data Collection

6.5.1 Phone Survey

Each participant will complete an automated phone survey (<3 min.) on a daily basis, which will capture data related to product use/nonuse behaviors and sexual behaviors. The automated system will call the participant every day at the same number and time (the number and time will be provided by the participant at V2, and can be updated upon participant request throughout the study as necessary). Daily phone surveys will occur every day starting the day the participant enrolls in the product evaluation study (V2) and continuing until Visit 5 has been completed, or they have/are withdrawn from the study. Collecting phone survey data daily will allow us to capture data on typical sexual behaviors, as well as any potential compensatory behaviors that can be queried during the IDI (e.g., changes in sexual activity, frequency, use/non-use of non-study products; see §6.5.3). If the participant does not answer the call from the automated system, a message will be left instructing the participant to call in to the phone survey system. If a participant does not complete a phone survey on a given day, the study team will be notified automatically by email and will then contact the participant to follow up.

The phone survey will capture basic variables that allow the survey system to prompt the user to complete a web-based survey when applicable, and to monitor for any adverse events or participant concerns. Following a report of RAI (and, for women, VI) in conjunction with study product use, participants will be prompted to complete a web-based survey regarding their experiences both with insertion of the product and in the sexual encounter. (See APPENDIX: Questionnaires: Daily Phone Survey).

6.5.2 USPE Product Evaluation: Web-based survey

Web-based surveys (~30-45 minutes) will include USPE items and scales, conventional acceptability questions, and behavioral and psychosocial measures capturing participant experiences during RAI/VI (e.g., partner type; sexual behavior; product use self-efficacy; willingness-to-use product). Additionally, participants will be asked open ended questions about what they liked/didn't like about the product, and any other recommendations that they might have. These answers may be used to remind participants of salient experiences to be discussed further during the in-depth interview (IDI, see section 6.4). After completing the sex-associated web-based survey, participants will be prompted to schedule their next study visit. Following completion of the final questionnaire, participants will complete a face-to-face qualitative in-depth interview (IDI), with survey item evaluation elements as applicable.[32] The IDI will focus on a discussion of the participant's use experience and the factors that impacted that experience, including product factors and the interaction of product experience factors and other use factors (timing of application, sexual behavior sequencing, etc). Data will be collected regarding participants' experiences of each of the salient dimensions of sensory perceptions and product characteristics. The web-based survey will include scales adapted to capture the RAI and VI experiences using suppository formulations. In addition, the web-based survey will include other items relevant to sexual behavior and prevention, such as partner perception items. The survey system presents each item and its potential responses as a separate screen. USPE items are divided into two sections: insertion/application experience and RAI/VI experience (as applicable). Remaining items are positioned before and after USPE sections, as applicable.

The Perceptibility scales administered to participants in this study consist of statements (i.e., items), written in a factual tone, to which participants respond with varying levels of agreement (i.e., 1=Do Not Agree at All; 2=Agree a Little; 3=Agree Somewhat; 4=Agree a Lot; 5=Agree Completely). Scales are used frequently in psychological and social sciences to quantify experiences across participants, and to predict specific outcomes. Each item is designed to capture a specific construct, concept, or experience targeted in the study. In scale development, several items represent similar experiences, and can appear redundant to a participant (participants are instructed to read each item as a stand-alone experience and respond as such). These seemingly redundant items (i.e., as seen at face value) may actually be capturing underlying latent constructs that differ from each other. Scales often represent underlying constructs that are not necessarily identifiable at face value. Until the psychometric analyses are complete, the generation and evaluation of redundant items is critical to the development of reliable and valid scales. Ultimately,

with careful psychometric and conceptual analyses, scales will be finalized that lack redundancy and that capture experiences that are either mutually exclusive or that correlate with each other in consistent ways, but are not overlapping.

Each scale has a different number of items, and, therefore, a different potential score range. In interpreting each scale score, averaged item means will be considered as an indication of the overall disagreement-agreement for each scale. Thus, the item mean represents the general level of agreement the sample endorsed with respect to a given formulation experience. Female vaginal scales (from which the rectal scales were derived) were psychometrically validated in the Microbicide Innovation Program studies (MH080591),[23] as well as another MIP award (R33AI076967), and preliminary analyses of the adapted rectal scales from Project 5.1 (evaluating gel/cream formulations) and Project 4 (volume comparison imaging study) have been completed (see §1.1.1. *The Current IPCP's Progress in Rectal and Dual Compartment Perceptibility*). Comprehensive psychometric validation of the rectally-adapted scales cannot be accomplished until larger data sets can be accumulated: the DRUM-S data will be included in future validation analyses.

Scale items are organized within the questionnaire by the logical progression of activities in which a participant engages, or in which s/he experiences the products and study activities. The USPE scales used in this study fall into two broad categories, each of which is associated with a different product evaluation experience. The categories, as well as descriptive titles of the scales within each category, are as follows:

Application (Insertion) / Ambulation: Descriptive titles of the scales pertaining to the Application and Ambulation experience of participants are: Application Leakage; Application Ease; Application Discreet-Portable; Application Product Awareness; Application Lack of Awareness; Ambulation Product Movement; Ambulation Leakage; Ambulation Hygiene; Ambulation Stickiness; Ambulation Awareness; Ambulation Spreading Behavior[23]

Sexual Activity: Descriptive titles of the scales pertaining to sexual activity are: Sex: Initial Penetration; Sex: Initial Lubrication; Sex: Spreading Behavior; Sex: Product Awareness; Sex: Perceived Wetness; Sex: Stimulating; Sex: Messiness; and Sex: Leakage.[23] Additional scales are being preliminarily validated in another of the IoR's studies, and will be evaluated here, as well. They include: Sex: Naturalness; Sex: Lubricity; Sex: Effortful; Sex: Pleasure; Sex: Precoital Leakage; and Sex: Noticeable

As part of their final web-based USPE survey after evaluating all three study products, participants will complete a final acceptability survey. This survey will focus on participants' preferences for study products, and will capture both a ranking of the study products and a forced choice. This approach will allow more nuanced comparisons across products and indications of willingness-to-use associated with each product.

In addition to the scales enumerated here, the overall measurement development activities include additional items that, alone (i.e., not as scale items), have shown significant differences in user experiences between vaginal gels with varying physicochemical and rheological properties. These items are also part of the current study's survey. It is hypothesized that these items capture unique constructs not fully captured within the parameter space of earlier studies and that they will either do so again, or, as a function of the current study's dosage form properties and the RAI/VI experience, begin to correlate and form new scales.

6.5.3 Qualitative In-Depth Interview Agenda

Questions for the IDI agendas have been derived from 1) extensive review of the formulation acceptability literature, 2) investigators' prior experience with user perceptibility studies and hypothesized correspondence with biophysical properties and functionality, and 3) the accumulation of knowledge

gained from our ongoing formulation perceptibility studies (including Project DRUM/5.1 and Project 4). Questions and probes are structured accordingly. A semi-structured qualitative agenda ensures that facilitators gather data across the same dimensions regarding biophysical properties and rheological performance of the dosage forms and their potential correspondence to user perceptions. The agenda is written to assist the facilitator but is not a rigid script that must be adhered to. This ensures that each facilitator gathers data on the same topics, but affords flexibility of natural narrative conversation to pursue a priori topics, as well as emergent themes as encountered.

The agenda includes discussion of the participant's perceptions of the products, while gathering data on the language s/he uses to describe it. Lines of inquiry will include participant perceptions and thoughts regarding the applicable salient dimensions of sensory perceptions and product characteristics: experiences of leakage (or dryness), for example, and what degree of leakage (or dryness) is tolerable versus not; how use of each formulation influences sexual pleasure and/or comfort during sex; perceptions of ease of insertion, dosage form volume considerations, and implications for covert use when using each dosage form. Participants will be asked to: a) discuss any steps they take to prepare for anal or vaginal intercourse (e.g., douching, enema, lubricant use), b) discuss their perceptions of the product insertion process, including its ease or difficulty, b) describe if, when, and under what conditions each product leaked out of the rectum/vagina, c) describe awareness of the product during RAI/VI, including perceptions of presence/absence, moisture, wetness, dryness, etc., d) discuss product behavior as it impacts the experience of sex, including lubrication or desiccating properties, perceptions of interference, sexual pleasure and/or comfort, etc., including the product's impact on use of sex toys, if applicable; e) consider whether the products might be used covertly, and f) discuss volume considerations in the context of RAI. Throughout, the participants will be asked to assess both positive and negative aspects of product characteristics and behavior. The goal is to establish an understanding of the potential correspondence between product properties and functionality, users' perceptions of the behavioral dimensions of interest (listed above) and to assess if any new experiences or domains exist for suppository formulations. For female participants, an additional line of inquiry will be to discuss how RAI is perceived in context overall, and how using such a product for RAI, VI, or dual compartment protection may impact sexual sequencing and her overall sexual experiences. Participants' assumptions or opinions about how their sexual partners may have experienced the products will be an element of the discussion, if appropriate.

As IDIs are completed, the research team will review constructs/concepts addressed and the language participants use to describe their sensory perceptions and experiences. These constructs/concepts and language will be used to further adapt existing items as necessary and generate new items unique to the suppository use experience and the interplay between RAI and vaginal sex (for female participants).

Study Completion Debriefing

At the end of the final visit (Visit 5), after all study-related activities have been completed, each participant will be debriefed by study staff. The debriefing will consist of thanking them for their time and effort in completing the study, and reminding them of the study purpose. In particular, the study staff will remind the participants of the challenge of developing effective HIV prevention products and that it is critical that a product be safe, effective, and acceptable. An acceptable product is one that will be used correctly and consistently (i.e., adherence); thus it is important that it have a neutral impact on the sexual experience, increase comfort/pleasure during RAI/VI or, at a minimum, not increase discomfort. Their efforts in this study will help scientists design a (dual compartment) microbicide that elicits these USPEs, so that the goal of reducing the HIV/AIDS pandemic can be realized.

7. Safety

7.1 Clinical Management of Adverse Events

7.1.1. General Adverse Events

By definition, an adverse event can be either a new finding or symptom, or a worsening of a pre-existing condition. In order to accurately capture adverse events in follow-up, all volunteers will be clinically screened, and a medical history obtained by the study clinician at V1, before enrollment in the product evaluation portion of the study. Adverse events (e.g., fever, pain) will be elicited during the daily phone survey and during study visits. Referral to appropriate care will be offered to participants as needed. Criteria for product hold for AEs, and for discontinuation of an individual's participation in the study are described below.

While the two OTC study products and the HEC placebo gel are overall considered safe, side effects or adverse events are possible and could occur in the context of any of the three product evaluations. Self-administration of study product could result in trauma to the anus, rectum, vagina, or genitals. In addition, side effects, including itching, burning, redness, rash or hives, are possible with any rectal or vaginal product use. Participants might also experience pain and/or discomfort during RAI/VI itself.

Should an adverse event or side effect be reported, study staff will first collect relevant information and contact the study clinician to determine whether the participant will be seen immediately or referred to her/his personal physician. If the event does not require immediate triage or treatment, study staff (or the study clinician) will discuss a plan, or any alternative referrals, and, if applicable, request that s/he sign a Release of Information form so that study staff can follow up on the event through resolution. Study staff will complete a follow-up phone call with the participant within 72 hours, to determine whether the event has been resolved, whether treatment was sought, what treatment was provided, and any other information that would 1) assure the participant has been properly treated, and 2) help to categorize the event for AE reporting purposes. Staff will continue to follow up with the participant until adequate resolution can be verified. If staff or the participant finds it necessary, referral back to the study clinician will be made promptly.

7.1.2 Pregnancy

Pregnancy during study participation is unlikely due to the requirement for effective contraception. However, urine pregnancy tests will be performed during each study visit for all female participants.

If a female participant has a positive pregnancy test, she will be referred via the study's clinician to appropriate care of her choice, inside or outside the Miriam Hospital/Lifespan network.

7.1.3 HIV Infection

HIV testing is scheduled at the Screening Visit. HIV pre- and post-test counseling will be conducted by clinical staff, or non-clinical research staff trained in HIV/STI/hepatitis counseling and testing by the Rhode Island Department of Health. Research staff conducting rapid HIV counseling and testing will communicate non-reactive results to participants as well as the study clinician. If a participant's result is reactive, he or she will be referred to the study clinician for follow-up confirmatory testing and referrals as appropriate. If a participant's result is invalid, study staff will run a second rapid test. The State of Rhode Island Department of Health (RIDOH) requires the reporting of positive test results for: Neisseria gonorrhoea, chlamydia trachomatis and syphilis within 4 days of diagnosis and HIV/AIDS within 14 days of diagnosis.

7.1.4 Criteria for Discontinuation

Participants may voluntarily withdraw from the study for any reason at any time. The Site PI/designee or study clinicians 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. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, including the Office of Human Research Protections (OHRP), or site IRBs terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing Visit 5. Study staff members will record the reason(s) for all withdrawals in participants' study records.

Product Hold

Product holds are not anticipated as this study involves single exposures to each of the three study products, none of which contain anti-HIV agents. If a Grade 2 or higher AE occurs, the PSRT will meet to discuss participant care/referral, any additional product or procedure revisions/resolutions, and to determine study status overall should the event be deemed related to product use.

Permanent Study Product Evaluation Discontinuation

The criteria for permanent discontinuation of further study product evaluations for an individual participant are:

1. Pregnancy
2. Request by participant to terminate study product
3. Clinical condition(s), which in the best judgment of the study clinician, are believed to be harmful or potentially life-threatening to the participant, even if not addressed in the AE management section of the protocol
4. Recommendation by the IRB, PSRT, DAIDS Medical Officer, OHRP, or FDA

The participant will continue to be followed with his/her permission if study product is discontinued. No subsequent modifications to the visit schedule and duration of continued follow-up will be made, except for discontinuation of the study product. Any participant withdrawn due to pregnancy will be followed for pregnancy outcomes, with her permission.

Participants who have not engaged in RAI/VI with study products and completed a web-based survey (i.e., product evaluation activities) after ~10 days will be contacted by the study team to ensure that they understand the study requirements and are still willing and able to comply. If a participant still has not completed product evaluation activities after ~20 days, they will be contacted again by the study team to again discuss whether they are willing and able to continue participating in the study. If a participant has not completed a product evaluation web-based survey after ~28 days, they may be withdrawn from the study (at the discretion of the PI or designee, depending on the individual circumstances of the participant). Participants who voluntarily withdraw from the study or who are withdrawn for safety or protocol compliance reasons will be replaced, if the study timeline allows. That is, given study timeline availability, additional participants will be enrolled to reach approximately 20-30 completed participants.

7.2 Safety Monitoring

The study investigators and clinicians are responsible for continuous close safety monitoring of all study participants, and for alerting the DAIDS Medical Officer and IRB if unexpected concerns arise. The IoR or designee, the study clinician, the DAIDS Medical Officer, and an IPCP Co-I will serve as the Protocol Safety Review Team (PSRT), along with a clinician not involved in the study. If necessary, external experts representing expertise in the fields of behavioral science, microbicides, and medical ethics may be invited to review the events. The PSRT and the study team will cooperate closely to monitor participant

safety and respond to potential adverse events in a timely manner. Study staff will seek to maintain close and effective communication with study participants and communication with and cooperation among study staff, investigators, the PSRT, and the DAIDS Medical Officer.

7.3 Clinical Data Safety Review

The Project Director (or designee) will generate data summaries on a monthly basis for IoR and Study Clinician review. These data summaries will consist of adverse event, accrual, and retention data. The study clinician (or designee) will evaluate adverse event data independently and present those to the PSRT for review, as necessary. If more urgent safety matters arise, the PSRT will meet emergently to determine a course of action. The PSRT will determine whether or not the study protocol should continue as originally designed, should be changed, or should be terminated.

The TMH IRB will be notified of any serious and unexpected adverse events according to the policies outlined in the Miriam Hospital IRB Policy and Manual of Operations. The following information will be submitted to The TMH IRB at the time of renewal of a research protocol, as required by IRB guidelines:

- The frequency of monitoring during the renewal interval, including the dates of data and safety monitoring;
- A summary of any assessment performed to evaluate external factors or other relevant information that may have an impact on the safety of study participants or the ethics of the research study;
- A summary of the outcome of procedural reviews conducted to ensure subject privacy and research data confidentiality;
- Any conclusions regarding changes to the anticipated benefit-to-risk ratio of study participation and final recommendations related to continuing, changing, or terminating the study, with accompanying rationales as appropriate.

7.4 Adverse Event Procedures and Reporting Requirements

7.4.1 Adverse Events Definitions and Documentation

An AE is defined as any untoward medical occurrence in a clinical research participant administered a study product and which does not necessarily have a causal relationship with the study 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 a study product, whether or not considered related to the product. This definition is applied to all participants beginning from the time of first product use. The term "study product" for this protocol refers to HEC gel inserted with the HTI Comfort Tip® applicator, Key-E® suppository, Zetpil® suppository.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences that they may experience, except for possible life-threatening events, for which they are instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation at The Miriam Hospital, where the study clinician is based, and to request that a study clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained for review. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes over a 72-hour period.

Study staff will record in source documents all AEs reported by, or observed in, enrolled study participants regardless of severity and presumed relationship to study product. For each study participant, AE documentation and reporting will be undertaken throughout the scheduled duration of follow-up.

Complete descriptions of all AEs will be entered in source documents, and will include:

1. AE term (i.e., the one term that best describes what occurred)
2. AE start and stop dates
3. Severity grade of the AE (see grading table information)
4. Study product(s) administered
5. Relationship of the AE to the study product(s)
6. Action taken regarding the study product(s)
7. AE outcome (e.g., recovered or resolved, not recovered or not resolved, recovered or resolved with sequelae, or unknown)
8. What seriousness criteria, if any, were met

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

- AE severity will be graded per the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, Nov 2014, and the following addenda to this table: Addendum 1 Female Genital Grading Tables for Use in Microbicide Studies Version 1.0, November 2007 (Clarification dated August 2009), with exception of asymptomatic BV not being considered AE), Addendum 2 Male Genital Grading Table for Use in Microbicide Studies Version 1.0, November 2007 and Addendum 3 Rectal Grading Table for Use in Microbicide Studies Version 1.0, December 2004 (Clarification dated May 2012). AEs not included in the Male/ Female Genital Grading Scale or Rectal Grading Table for Use in Microbicide Studies will be graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014]. In cases where a genital or rectal AE is covered in both tables, the Female Genital or Rectal 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, and the clinical judgment of the study clinician/PI/designee. The study products that must be considered when AE relationships are assigned are HEC gel, HTI Comfort Tip® applicator, Key-E® Natural Vitamin E suppositories, and Zetpil® suppository.

The DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0. [November 2014] is available on the DAIDS Regulatory Support Center (RSC) web site: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf. The Rectal Grading Table for Use in Microbicide Studies and both the Male the Female Genital Grading Tables for Use in Microbicide Studies, are available via links in that document on page 9.

7.4.2 Adverse Event Follow-Up and Management

For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant's study exit visit, the study clinician/PI/designee must establish a clinically appropriate follow-up plan for the AE and review with the DAIDS Medical Officers. At a minimum, the AE must be re-assessed by study staff at least 2 weeks after the participant's final visit; additional evaluations also may take place at the discretion of the study clinician/PI/designee. The same approach must be taken for any AEs deemed related or possibly related to study product that are found to have increased in severity at the final study visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date, and referrals for additional care will be provided if appropriate.

7.4.3 Adverse Event Reporting to DAIDS

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS are: HEC gel, HTI Comfort Tip® applicator, Key-E® suppository, and Zetpil® suppository.

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, dated January 2010, which is available on the RSC website (http://rsc.tech-res.com/safetyandpharmacovigilance/). The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about DAERS, please contact the NIAID CRMS Support at NIAIDCRMSSupport@niaid.nih.gov.

AEs will be reported to the DAIDS Medical Officer within 24 hours of the investigator becoming aware of the event during the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason). Additionally, the Investigator of Record (IoR) or designee will log any and all adverse events to the DAIDS Medical Officer on a monthly basis, regardless of expectedness or relationship to study product use. Furthermore, the local IRB categorizes AEs and the relationship to study product as follows: 1) definitely related, 2) probably related, 3) possibly related, 4) probably not related, and 5) not related. The IoR or designee will report all AEs in categories 1 and 2 to the DAIDS Medical Officer as related to the study product. The IoR or designee will report all AEs in categories 4 and 5 to the DAIDS Medical Officer as not related to the study product. Additionally, all AEs in category 3, defined by the local IRB as possibly related, will require consultation with the DAIDS Medical Officer in order to determine if the AE is categorized by DAIDS as related or not related to the study product.

After the protocol-defined AE reporting period, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4.4 Adverse Event Reporting to Local IRB

The study site investigator will report adverse reactions to the responsible IRB (The Miriam Hospital) in accordance with respective IRB policies and procedures, as follows.

The Principal Investigator/IoR must report to the institutional IRB (i.e., The Miriam Hospital (TMH) IRB) those problems or adverse events that: 1) are unanticipated, 2) involve increased risk to participants or others, and 3) are more likely than not related to the research activity being conducted in the present protocol.

> ***Serious Unanticipated Problems/Adverse Events*** that meet the reportable criteria above and are more likely than not, probably, or definitely related to the research activity, will be reported to the TMH IRB within 5 working days of the date the investigator becomes aware of the event.
>
> ***Deaths***, whether related or unrelated, will be reported to the TMH IRB and DAIDS MO within 24 hours of the investigator becoming aware of the event. This 24 hour notification may be via phone, fax, email or report form and should be followed by a written report as soon as possible.

Serious Unanticipated Problems/Adverse Events that are possibly related to the research activity will be reported to the TMH IRB promptly, within 30 days of the investigator becoming aware of the event; or within the timeframe as required by the sponsor, whichever comes first.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the study site investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting, the study site investigator will report it as soon as possible in accordance with respective IRB policies and procedures.

8. Data Analysis Considerations

8.1 Overview and General Design Issues

As noted earlier, this study is a formative mixed-methods design. Both quantitative and qualitative data will be collected. Quantitative data will consist of participant responses to prescreening questions, as well as their responses to phone, web, and CASI questionnaire items. Qualitative data will consist of narrative data recorded and summarized/transcribed as part of individual in-depth interviews.

8.2 Study Endpoints

8.2.1 Primary Endpoint

1. Generate adapted and novel rectal USPE items to be used in evaluating the perceptibility, user experience and acceptability of rectal and dual compartment topical formulations, as proposed in the parent grant.
2. Characterize USPEs of gel and suppository formulations used for RAI and VI using both existing and novel USPE items/scales.

8.2.2 Exploratory Endpoints

3. Collect participant-reported information regarding the safety of the suppository forms. The information collected will include any adverse events (and their severity grading) deemed to be related to the suppository dosage form by the study clinical staff and/or in consultation with the Medical Officer.
4. Identify formulation-specific classes of USPE scale scores (Sex-associated scales): by sex (males, females), by compartment (Rectum: males and females. Vagina: females), resulting from Latent Class modeling analyses, given adequate final evaluable sample sizes.

8.3 Other Study Design and Data Considerations

8.3.1. Formative Research Questions

Given the formative nature of this stage of study, standard hypothesis testing is not an appropriate endpoint. In general, the study will identify, characterize and illustrate the range of USPE scale scores across several sensory perception domains, both between and within formulations (gel; suppository).

8.3.2 Sample Size Considerations and Participant Stratifications

The study will enroll approximately 20-30 individuals who practice RAI (~10-15 males; ~10-15 females). Recruitment of all participants in the study will be designed to provide a range of individuals, varying in age and other baseline characteristics, in order to gather qualitative data from individuals representing a variety of perspectives. Each participant will be randomly assigned to experience the products in one of six possible orders of product evaluation experiences. Qualitative studies proceed until no new data emerges, i.e., to saturation, which involves eliciting all forms or types of product-related experiences.

Based on prior experience, it is expected that saturation will be attained in this study within ~6-10 male and ~6-10 female individual in-depth interviews: however, we will continue with the full sample enrolled until data redundancy is achieved.

8.3.3 Statistical Considerations

Given the planned sample size (n~20-30), and the formative nature of this research, statistical comparisons between products are not the most important aim of this study. However, assuming the larger sample size (i.e., 24-30, 12-15 males and 12-15 females) is achieved and conditions for USPE scale comparisons are met (i.e., analyses indicate good psychometric properties of existing scales, such that we confirm each scale's internal validity by verifying high item scale loadings and we find good internal consistency for a specific scale as measured by the Coefficient Alpha statistic), we will compare products and compute the effect sizes for all of the comparisons of each formulation between sexes (i.e., given 12-15 males and 12-15 females), between compartments (females), and between formulations to provide guidance for outcomes interpretation and for future studies. While we do not expect all comparisons between products to be statistically significant as the relatively small sample size places limits on statistical power, we do anticipate that some comparisons may be statistically significant based on our past research into scale score comparisons conducted on a number of different products. For example, with respect to sexual activity scales in our previous study among a sample of 24 heterosexual couples using vaginal formulations and engaging in vaginal-penile sex, effect sizes resulting in significant differences in pair-wise comparisons of 3 different formulation conditions ranged from 0.60 (considered a medium effect size) to 2.67 (considered a very large effect size). In Project DRUM (section 1.1a), among a sample of 15 (8 male; 7 female) participants using rectal formulations and engaging in receptive anal intercourse, effect sizes ranged from small to medium.

8.3.4 Planned Interim Analyses and Qualitative Study Saturation

In a timely manner after each participant's qualitative interview (Visit 5), facilitators will conduct reviews of the audio recordings. This process is considered a preliminary analysis of the qualitative findings. The major objective for this interim data review is to summarize key findings from each interview, and list concepts, patterns and themes discussed. These findings may be incorporated into future interviews to gain greater depth or clarity of understanding, as is typical in qualitative methodology.

Should concepts, patterns and themes become redundant (i.e., no new information emerges) as interviews within female and male participants are completed, investigators will consider whether data collection has reached saturation and can cease. Given adequate recruitment, a minimum of 7-10 female and 7-10 male qualitative interviews will be completed, as, across our experience, it is likely to be the minimum for determining saturation.

8.4 Data Analysis

a. Qualitative data will be systematically reviewed to characterize and better understand the experiences and perceptions of female and male participants using the three formulations, as well as used to generate new items for formulation evaluation tools (i.e., if conceptual gaps are identified). We will also complete content and thematic summaries of the qualitative data to identify themes and patterns of perceptions and opinions that can help investigators understand the range of user perception issues pertinent to suppository formulations.[33]

b. Questionnaire data (e.g., demographic; sexual/reproductive history variables) will be used to describe the complete and evaluable samples, and may be used (e.g., USPE scale scores and their statistics; willingness-to-use; pairwise comparisons) to stratify participants in the qualitative data to determine whether themes and patterns vary as a function of those variables.

8.4.1 Qualitative analyses

Qualitative data will be systematically reviewed to characterize and better understand the experiences and perceptions of female and male participants using the three formulations, as well as used to generate new items for formulation evaluation tools (i.e., if conceptual gaps are identified). We will also complete content and thematic summaries of the qualitative data to identify themes and patterns of perceptions and opinions that can help investigators understand the range of user perception issues pertinent to suppository formulations.[33]

Each qualitative in-depth interview will result in an audio recording, a written matrix summary, and a transcript. Quantitative data, gathered from the phone, web, and CASI surveys will be used to describe and potentially stratify the sample of participants, employing variables such as age, race/ethnicity, frequency of RAI, etc.

Qualitative data collection will focus on participants' sensory perceptions and formulation experiences. Data collection overall will focus on participant descriptions of the sensations they experience, what those sensations mean, how they relate to willingness to use the products being evaluated, and the language participants use to describe the sensations and meanings ascribed to those sensations. The primary focus for all participants will be on the experience of RAI/VI with each formulation. Given the formative nature of this stage of study, standard hypothesis testing is not an appropriate endpoint. Characterization of the sensory experiences of both male and female users, via both the quantitative scale scores and the narrative qualitative data, is the goal.

The matrix summaries will focus on the dimensions of perceptibility under investigation including: a) the insertion process, including its ease or difficulty, b) conditions under which each formulation leaked out of the rectum/vagina, c) participant awareness of the product during intercourse, including perceptions of presence/absence, moisture, wetness, dryness, etc., d) impact of product behavior on sexual intercourse, including lubrication or desiccating properties, perceptions of interference, sexual pleasure and/or comfort, etc., e) consideration of possible covert use, and f) volume-related considerations in the context of RAI and, g) for female participants, dual compartment use. Primary data analysis will include a summarization of the range of experiences participants reported on these dimensions, a consideration of whether new perceptibility issues arise specific to the suppositories used in this investigation, and an evaluation of new quantitative items for the tool that represent semi-solid or solid (suppository-specific) perceptibility. Matrixed summaries will be produced by facilitators who review each audio recording and complete summaries identifying and discussing themes and dimensions of interest, both those that recur across multiple interviews and those that represent divergent or minority points of view.

After primary (matrix) data analysis is complete, continued in-depth analyses of the qualitative data collected during this project will be important to our ongoing efforts to better understand formulation perceptibility and how perceptibility (and potentially acceptability and adherence to product use) is impacted by user sensory perceptions and experiences of formulation properties, and in particular, with respect to suppository forms. Therefore, transcripts of qualitative data will be analyzed using thematic analysis in which a coding scheme is developed based on the initial analysis, the study aims, relevant literature, and knowledge gained as a function of the IoR's other ongoing perceptibility projects. Qualitative data analysis is an iterative process that allows for new ideas and concepts to emerge and be integrated into the overall conceptualization of the results. In this process, passages in the transcript text that represent areas of particular interest are identified with codes (some of which will be used in reports and manuscripts, once de-identified, as illustrative text). Coders will independently review each transcript to identify those passages (a minimum of 25% of transcripts will be independently coded by 2 coders: codes will be compared, discrepancies will be discussed, and agreed upon (i.e., master) codes will be entered into the qualitative data base). Coded data will be summarized by investigators, accounting for

and interpreting major themes and perceptibility dimensions, relationships with other codes, themes, and dimensions, and relationships with quantitative variables, and, in particular, key formulation dimensions of interest. An analysis of these qualitative data will be completed as soon as possible after initial analysis is concluded. Investigators will refer back to qualitative data after quantitative analyses have been completed, providing an opportunity to expand upon the ways in which we understand how participant sensory perceptions and experiences interact with product properties and how variations in those properties can result in variations in user-derived meanings, thus integrating the qualitative and quantitative components of this project.

8.4.2 Quantitative Analyses

Psychometric and Validity Analyses

Psychometric analyses of the responses of the expected ~10-15 male and ~10-15 female participants who will complete evaluation of the three products will be conducted. We will start the analyses by examining the individual item characteristics for items that have been adapted from our previous USPE scales for use as rectal USPE scales to measure the products used in this trial. We will first conduct an initial examination of means, standard deviations and endorsement level for each item. We will then examine the component structure (internal validity) of each of the adapted scales using principal component analyses to conduct these exploratory dimensional analyses. We will also calculate internal consistency values (Cronbach's Coefficent Alpha statistic) for each of these newly adapted scales for each of the evaluated formulations. In addition, we will conduct exploratory dimensional analyses using principal component analysis to examine the additional items that have been added to the original pool of items in anticipation of unique physicochemical and rheological properties hypothesized to be associated with the rectal environment and suppository formulations, and also to measure any hypothesized USPE scales that we expect to be unique to these experiences. These analyses may result in new and unique additional USPE scales. A series of paired sample t-tests comparing each product pair will then be conducted on the scores from all USPE scales for the males and females separately, and also as a combined sample. See section 8.2.4 and 8.2.5 for associated effect size and power analysis considerations.

Sociodemographic and Individual Product Comparisons

We will first provide an overall description of the sample of participants using means, standard deviations and percentages, as appropriate, to examine demographic variables such as age, sex, and race/ethnicity, as well as sexual/reproductive history variables. After conducting the psychometric analyses, we will also calculate scale scores associated with the USPE scales being evaluated and compare them as noted in 2.1.1(2) above. These scores will be considered in relation to the biophysical measures associated with the formulations being evaluated. Specifically, we will quantitatively examine responses on the pre-existing and adapted/new user perception scales, within both females and males, for perceptual differences between products on the different scales using paired t-tests. Given our small sample size and the new context of the study parameters, we will not apply a correction for the number of statistical tests conducted, to guard against Type II statistical errors. We will also calculate effect sizes for each product comparison as a Cohen's *d* statistic.[34] Secondary analyses that examine group differences (e.g., age, race/ethnicity, etc) across behavioral dimensions and formulation ratings will also be conducted, using independent t-tests, analysis of variance, and Pearson correlations, as appropriate, and as data allows. Further, other quantitative data may be used (e.g., USPE scale scores and their statistics; willingness-to-use; pairwise comparisons) to stratify participants in the qualitative data to determine whether themes and patterns vary as a function of those variables.

9. Data Handling and Record Keeping

9.1 Data Management and Storage

9.1.1 Prescreening data, STI/HIV/Pregnancy Results, Participant Enrollment and Completion Log

The study team keeps a password-protected participant log (Microsoft Access) that stores prescreening (eligibility) data by unique Research Identification Number (RIN), linked to participant initials (FML or F-L), as well as process data such as when (i.e., date) the participant signed a written ICF and HIPAA approval, whether and when the participant completes each visit and/or survey, and whether s/he had received his/her compensation. This file is password protected on the project-specific drive of the hospital's server. It is used to ensure our ability to properly audit individual eligibility, consent, and research activity completion and is required by our institution. Prescreening data is used to document eligibility for the study: process data are used for auditing purposes. No data from the process log is used in any study-related analyses.

Positive STI results, including reactive HIV rapid test results, will be communicated to the participant by the study clinician, who will proceed with clinical management protocols or referral, as deemed necessary and agreed to by the patient. The State of Rhode Island Department of Health (RIDOH) requires the reporting of positive test results for: Neisseria gonorrhoea, chlamydia trachomatis and syphilis within 4 days of diagnosis and HIV/AIDS within 14 days of diagnosis. If an individual participant's pregnancy result is positive, she will be referred by the clinician to appropriate clinical follow-up and withdrawn from the study. No urine, blood or any testing materials will be stored once results have been read and reviewed by the study's clinician. The laboratory, not study staff, makes the necessary STI/HIV reports to the Department of Health, as delineated by law.

To provide the strictest controls on RIN-initial linked screening and processing information, the study team destroys the link as soon as possible. In the case of this study, once the final monitoring visit is complete and the study has been closed by the sponsor, all initials (FML or F-L) will be deleted from the log, so that only the RIN remains. Thus within 30 days of the close of the study and completion of final monitoring visit, all potential identifying links will be eliminated. At this point, the protocol will be terminated with the local IRB, and designated as de-identified data analysis only.

9.1.2. Demographic and Sexual/Product History Questionnaire Database

Once enrolled, each participant will complete a demographic and sexual/reproductive health history questionnaire via CASI (computer-assisted self-interview). These data will be used to characterize the sample and, potentially, stratify qualitative data in subsequent analyses. Select variables will be uploaded into the Attributes section of the NVivo project used to manage the qualitative data, so that stratifications of qualitative data can be completed. These data are stored in a password-protected NVivo database, on the project-specific drive of the hospital's server.

Following RAI/VI with each study product, participants will complete a web-based survey consisting of items measuring their USPEs with the study formulations. All responses will exist in a secure web-based study database. Once data collection is complete, data will be downloaded and stored in RIN-identified, password-protected databases for analyses.

9.1.3. Audio Recordings

Audio recordings of IDIs will be stored on the hospital's secured server (project-specific drive), which is backed up daily and is accessible only by approved project staff. Audio recordings will be destroyed at study's end and only the transcripts and/or summaries (identified by RIN) will remain, designated as primary data sources. Transcripts and summaries are managed by uploading them into NVivo, a secure

qualitative data management software program that allows narrative data coding and sorting for timely analysis.

9.1.4. Daily Phone Surveys and Web-based USPE Surveys

Data collected via daily phone survey and web-based USPE survey are stored on Microsoft's SQL Azure platform, which is a resilient and highly secure data center. Azure is Sarbanes-Oxley and SAS 70 Type I and Type II compliant, and holds an ISO 27001:2005 accreditation. The Windows Azure system is a PaaS provider that includes three core components: compute, storage, and service management.[35] These services allow developers to use the .NET framework, SQL Azure, and Azure Storage to create web applications hosted using Microsoft data centers around the world. Windows Azure has completed a SAS 70, Type II audit and has FISMA certification and ISO 27001 certification. Windows Azure Platform provides several security mechanisms to keep data protected. Researchers must authenticate with their Windows Live Identifier so as to correctly identify themselves as an authorized client to help prevent unauthorized access to backend systems. Data stored on the platform is encrypted *within* Windows Azure, so even a breach of their security systems does not make data stored by the application available. Each study's data is logically separated onto a different (virtual) volume so it is difficult to access another study's data. Data can be replicated at several locations so catastrophic failure does not imply data loss. Physical access is restricted to their data centers and redundant network and power systems minimize likelihood of intermittent failures.

9.2 Data Management Responsibilities

Data collection and management of overall study process and data collected by TMH staff (i.e., Prescreening data, STI/HIV/Pregnancy Results, Participant Enrollment and Completion Log; Demographic and Sexual/Reproductive Health History Questionnaire CASI Database; Audio Recordings and Transcripts/Summaries) is the responsibility of the research staff under the supervision of the IoR or her designee. The research team will maintain complete and accurate documentation for the study. All hard copy records are stored in locked file cabinets (separate cabinets for name- and RIN-identified files) behind a locked door. Electronic copies of STI test results are stored in a secure digital location on the hospital's server, accessible only to clinicians and research staff.

Daily phone survey and web-based USPE survey data collection and management is the responsibility of Kinetiq, Inc, as designated by the IoR.

Research staff will be responsible for collecting, entering, and properly storing prescreening and process data required for auditing, as well as, separately, responses to the CASI survey and the qualitative interview data. Kinetiq will be responsible for maintaining a RIN-identified database for all daily phone survey responses and web-based survey responses. Kinetiq will collect data and maintain the database until it is downloaded to the omnibus study database.

Trained members of the research staff will be responsible for the process of informed consent, and for assuring complete and accurate ICFs and participant compensation vouchers. Additionally, they will be responsible for instructing participants regarding study activities, monitoring survey completion, and conducting qualitative interviews.

Investigators, as designated by the IoR and Principal Investigator, will be responsible for reviewing summaries as necessary, and helping in the interpretation of qualitative and quantitative findings.

9.3 Interviewer Training

A day-long training will review research requirements (ethics, informed consent, documentation) and project-specific data collection and management. Further, a multi-day training will be completed by Research Staff, focused on implementation and processing of qualitative interviews. Training materials

are derived from earlier studies conducted by our research team, and include an overview of qualitative research methods, building qualitative interview agendas designed to explore the research questions of interest, in-depth interview facilitation skills, note-taking, completing structured audio matrix reviews, and coding and summarizing textual data. In addition, senior study staff (PhD-level) will listen to the qualitative audio recordings and provide ongoing supervision and facilitation skills review and support.

9.4 Trainee Involvement

The IoR is a K24 mid-career development awardee, senior research scientist, and faculty member: as such, she provides mentorship in qualitative and mixed methods to post-doctoral fellows and junior investigators in patient-oriented research. As part of the mentorship agreement for the K24 award, the IoR must involve mentees in her research studies as a mechanism for proper training of qualitative and mixed methods research skills. The IoR's mentees will be permitted to be involved – with participant permission – in participant study visits, including qualitative data collection, in order to observe facilitation skills and protocol management. Study participants will agree to trainee involvement (or not) as part of the informed consent process. Mentees will *not* be given responsibility for conducting visits: study staff will be present and will maintain that responsibility at all times. All mentees are certified in human subjects' protection and HIPAA compliance, following the same certification guidelines as the local study team. The IoR will submit to the local IRB, upon request, a listing of all mentees who may participate in study visits as part of their training plan. The listing will include their certification dates and affiliations and will be updated at least annually in accordance with IRB policy.

9.5 Source Documents

Primary data sources for this study include STI/HIV/pregnancy lab results, the quantitative database (i.e., responses to the PreScreen survey and CASI demographic and sexual/reproductive health history questionnaire identified by RIN only; data from USPE and daily phone surveys), verbatim transcripts (identified by RIN only) of in-depth interviews, and interview matrix summaries (identified by RIN only). Once transcribed, cleaned, and confirmed to be accurate, in-depth interview transcripts will serve as primary data sources and audio recordings will be destroyed.

10. Human Subjects Protections

The investigators will make efforts to minimize risks of use of these products to human subjects. Participants will take part in a thorough informed consent process throughout their participation in the study. Before beginning the study, the investigators will have obtained IRB approval. The investigators will permit audits by the NIH or any of their appointed agents.

10.1 Institutional Review Board/Ethics Committee

The Institutional Review Board (IRB) for the Miriam Hospital (TMH), as well as the IRB overseeing ImQuest, Inc. (Western IRB), will be responsible for human subjects oversight of the current project. The protocol as presented here, related informed consent documents, and study-related documents (e.g., the CASI and web-based surveys, the IDI agenda) will be fully reviewed and approved by the TMH IRB prior to implementation of the protocol. As with previous protocols, we anticipate that Western IRB will designate TMH IRB as the IRB of record for interim revisions, but will require initial and continuing reviews. IRB continuing review and approval will be obtained from the reviewing IRB at least once per year. If IRB approval expires (e.g., lapse in continuing review), all ongoing research activities will stop, unless the investigator determines that it is in the best interested of already-enrolled participants to continue their study-related activities. New participants will not be enrolled on the study until IRB approval to continue the research is obtained.

10.2 Special Populations

Study staff will offer screening to eligible women and men of all ethnic and racial groups. Members of the study staff are not seeking the screening or enrollment of adults in special or vulnerable populations.

Children

The NIH has mandated that children be included in research trials when appropriate. This study meets *Justifications for Exclusion* criteria for children under 18 years of age as set forth by the NIH. Specifically, "a separate, age-specific study in (adolescent) children is warranted and preferable" at a later time.

Prisoners

Prisoners will not be included in this study (for screening or enrollment). Any participants incarcerated during the course of participation in the study will not be followed during their incarceration, and will be discontinued from the study. Participants who have been released from incarceration and/or Department of Corrections custody (and no longer meet the definition of "prisoner") will be permitted to return for any protocol specified follow-up or safety visits per the guidelines of the local IRB.

Pregnant women

Pregnancy is an exclusion criterion. At the clinical screening visit (V1) and each subsequent visit, a urine pregnancy test will be performed on all women. During the informed consent process, women will be informed that the study products do not prevent pregnancy. All enrolled female participants will be required to be using an effective method of contraception, such as hormonal contraception, intrauterine device or sterilization. Women who become pregnant during the study period after exposure to study product will not be excluded from analysis.

10.3 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that all relevant parties abide by the principles of the Good Clinical Practice (GCP) guidelines of the ICH, and will adhere to DAIDS policies. The study will also be carried out in keeping with local legal requirements.

10.4 Informed Consent

Informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. The informed consent process will give individuals all of the relevant information they need in order to decide whether to participate, or to continue participation, in this study. Potential research participants will be permitted to ask questions and to exchange information freely with the study investigators. Only listed study staff may obtain informed consent from study volunteers. The investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

Staff will provide information to the potential participant about study purpose and procedures, potential risks and benefits, confidentiality (including that their responses will only be identified by a Research Identification Number (not their name or other identifying information), and compensation. After answering any questions the volunteer may have, staff will seek verbal consent from the volunteer to administer the PreScreener survey to determine initial eligibility. If the potential participant agrees to answer prescreening questions, this agreement will be documented as part of the CASI database.

When volunteers who meet initial eligibility requirements present for Visit 1, research staff responsible for obtaining written informed consent will review important study procedures and aspects of consent (i.e. voluntary nature of participation, confidentiality, right to withdraw, risks and benefits of participation, etc.) and answer any questions s/he may have. The participant will be reassured that the information to be

collected is solely for research purposes and will remain confidential within research project personnel. They will be informed that they will be compensated for their time and effort at the rates specified in the ICF. The participants will be informed of their right to refuse to answer any questions and their right to withdraw from the study at any time. Research staff are trained to obtain informed consent globally, and with specificity to each protocol. Regardless of presumed literacy level of volunteers, the informed consent forms are read aloud verbatim to each potential research participant. Staff stop minimally at the end of each section, and often more frequently during particularly complex sections, and provide a summarization of the section and allow an opportunity for potential participants to ask questions throughout the process. Each potential participant will be required to provide informed consent by signing, initialing, and dating the study's Informed Consent Forms (ICF) as per institutional protocol. The consent forms will be co-signed and dated by the research staff in the presence of the participant.

10.5 Risk/Benefit Statement

10.5.1 Risks

It is not expected that this trial will expose human subjects to unreasonable risk. The products used in this study are unlikely to cause side effects. However, unanticipated side effects including irritation, sensitivity, or allergic reactions may occur. None of the formulations contain anti-HIV compounds or drugs.

Discomfort or Injury due to Study Products or Procedures

Study Products. Participants will be asked to evaluate 3 study formulations: HEC gel, Zetpil® suppository and Key-E® suppository, none of which contain any anti-HIV compounds/drugs. Participants will be advised not to taste or ingest any of the products. The likelihood of risk due to allergy or sensitivity will be mitigated by asking all participants during study screening if they know or suspect that they are allergic to rectal or vaginal products of any kind, including lubricants, as well as all ingredients specific to the study products. Symptoms indicating general allergic reaction include: itching, burning/stinging, red or watery eyes, sneezing, runny nose, coughing, rash or hives, chest tightness, shortness of breath, or shock; symptoms indicating sensitivity to Zetpil® include nervousness, tremor, sleeplessness, nausea, loss of appetite. Symptoms typically appear within 12 to 36 hours after exposure. As symptoms can be serious, participants known to have rectal or vaginal product or lubricant allergies will be excluded from the study.

It is possible that participants will experience rectal/vaginal pain, discomfort, or trauma due to use of the HTI Comfort Tip applicator. To mitigate this risk, participants will be given detailed insertion instructions (including lubrication of the applicator) during the appropriate product provision visit. It is also possible that participants will experience rectal pain, discomfort, or trauma related to digital insertion of suppositories, including lacerations due to fingernails, hangnails, or jewelry. Participants will be provided with single-use non-latex gloves and encouraged to use these as they deem necessary when inserting the product digitally in order to minimize these risks.

Male condoms will be provided to participants at each product provision visit (V2-4). Some people may have latex allergies that are unknown to them at the time of enrollment. Symptoms indicating allergic reaction to latex include: itchy, red or watery eyes, sneezing, runny nose, coughing, rash or hives, chest tightness, shortness of breath, or shock. Sometimes people will get bumps, sores, cracks, or red, raised areas on their hands (or other body part that comes into contact with the latex material). Symptoms typically appear within 12 to 36 hours after contact with latex. The likelihood of latex allergy or sensitivity will be mitigated by asking all participants during study screening if they know or suspect that they are allergic to latex. As symptoms can be serious, participants known to have latex allergies will be

provided with non-latex condoms during their participation in the study's product evaluation component. Non-latex condoms also will be available to those requesting them due to preference.

Clinical screening. Volunteers being screened for eligibility will be tested for HIV and STIs (all volunteers) and pregnancy (female volunteers). Some of these tests involve the collection of a serum (blood) sample. Venipuncture is sometimes associated with discomfort. Phlebotomy may lead to discomfort, dizziness, bruising, swelling, and rarely, an infection at the venipuncture site. Examination of the rectum/vagina (including vaginal speculum exams) can be associated with discomfort or embarrassment. Additionally, participants may become embarrassed, worried, or anxious when receiving HIV counseling, or while waiting for their HIV and STI test results. All procedures will be overseen by study staff with years of experience performing these procedures and dealing with any issues or concerns volunteers may experience. All study staff who will be conducting HIV counseling and testing are certified in HIV/STI/hepatitis Counseling, Testing and Referral by the Rhode Island Department of Health, and will be available to help participants deal with these feelings.

Volunteers will be informed of the possibility that the testing process or test results may cause discomfort or concern. Should volunteers experience such discomfort, there are a number of standard clinical procedures in place that staff will initiate:

a. Prior to initiating any procedures, research staff or the study clinician will explain any and all testing procedures, results implications, etc, to the volunteers and answer all their questions regarding the test result and/or treatment options.

b. Research staff, including the clinical trials nurse, are trained in HIV/STI counseling, testing, and referral, and will follow standard procedures to support volunteers in crisis.

c. The study clinician and the IoR are both licensed health care providers with experience dealing with affect associated with positive test results. The Miriam Hospital has standard clinical crisis procedures that will go into effect if necessary.

d. Should an individual choose to inform a partner or partners of a positive test result, research staff will be available to provide any information and/or referral to the state's partner notification program, if needed.

e. All participants will be informed of their right to refuse testing and, if refused, will subsequently be withdrawn from the screening process.

Study Questionnaires. Participants will be asked to complete surveys capturing individual and relationship demographics, sexual behavior, and product history information, as well as complete user sensory perception and experience (USPE) scales and associated product-related surveys. Some product history items or sexual behavior items may cause discomfort due to their personal nature. During qualitative in-depth interviews, similar questions related to sexual behavior and how the study formulations were experienced may also cause discomfort due to their personal nature. All participants will be informed of their right to refuse to answer questions and pass on any activity or inquiry during their participation in the visits.

Research Related Injury. If a participant experiences a research injury, Lifespan or the study clinician will arrange medical treatment. Such treatment will be paid for as follows: If a participant has insurance and has a research injury that is not covered by the study, it is possible that some or all of the cost of treatment could be billed to their insurer. If the participant's health insurance will not cover such costs, it is possible s/he would have to pay out of pocket. In some cases, Lifespan might be able to help pay if the participant qualifies for free care under Lifespan policy. However, Lifespan has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering. The study

sponsor, NIH, does not provide for costs of treatment. There is no program for compensation either through Lifespan or the U.S. National Institutes of Health (NIH).

Social Impact/Social Harms

While we do not anticipate the occurrence of social impact events resulting from the study participation, individuals enrolled in this study may experience such problems. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that participants may experience stigmatization or discrimination as a result of being perceived as being at risk for HIV/STI infection. For example, participants could be treated unfairly, or could experience problems being accepted by their families and/or communities. Problems may also occur in circumstances in which study participation is not disclosed, such as impact on employment related to time taken for study visits.

In the event that a participant reports a social impact event, every effort will be made by study staff to provide appropriate assistance, and/or referrals to appropriate resources. Social impact events are documented and reviewed on a scheduled basis by the protocol team leadership with the goal of reducing their incidence and enhancing the ability of study staff to mitigate them when possible. All instances of relationship discord, threats of violence, or other social harms related to misinformation or stigma associated with the study will be addressed as per The Miriam Hospital's standard protocol, including referral to treatment sources, mental health support, and legal support as necessary. The study team keeps a Resource and Referral Guide for all health and human services in the local area that can be provided to those who need it.

Social impact events that are judged by the IoR/designee to be serious, unexpected, or more severe or frequent than anticipated, will be reported to the responsible IRB promptly, or otherwise in accordance with the IRB's requirements.

10.5.2 Benefits

This is a measurement development and formulation perceptibility evaluation study. Participants will experience no direct benefit from the use of the study products.

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of safe and effective products to prevent HIV transmission. Participants will be screened for sexually transmitted infections, including HIV (and pregnancy for women). Participants can benefit from knowing their test results and receiving pre- and post-test HIV counseling, as well as referrals to local organizations for prenatal care, STI/HIV treatment and/or prevention and support. Additionally, by participating, participants will be helping researchers to evaluate and design acceptable prevention products that may help protect women and men against HIV and other sexually transmitted infections. The research staff will be available to answer any general questions participants may have about HIV/STIs, hepatitis or pregnancy prevention or treatment, and to refer them to additional resources, as necessary.

10.6 Compensation

Participants will not be charged for any of the study visits, study supplies, or examinations. There are no costs to participants in this study other than their time. Given IRB approval, participants will be compensated for their time and inconvenience while participating in the protocol. Compensation for study activities completed will be provided at each visit. In addition a parking pass will be provided to participants as needed.

10.7 Participant Confidentiality

Members of the study staff are all trained in maintaining the confidentiality of study volunteers and participants. All participant-related information including case report forms, laboratory results, evaluation forms, reports, etc., will be kept strictly confidential, as follows. Participant data will be identified only by a unique research identification number (RIN) that is assigned when prescreened for the study. RINs will not be reused should someone prove ineligible or choose not to participate.

All hardcopy records (RIN-identified) will be kept in a secure, double-locked location and only research staff will have access to the records. Participant informed consent forms (ICFs) and locator information (name, contact information) are securely stored separately from data files. Computerized databases will be password-protected. A password-protected participant log (Microsoft Access) that stores prescreening (eligibility) data by unique Research Identification Number (RIN), linked to participant initials (FML or F-L), as well as process data such as when (i.e., date) the participant signed a written ICF and HIPAA approval, whether and when the participant completes each visit and/or survey, and whether s/he had received his/her compensation is maintained by study staff. This file is password protected on the project-specific drive of the hospital's server. Upon request, participant records will be made available to the study sponsor, the sponsor's monitoring representative, and applicable regulatory entities. No identifying information will be revealed in any scientific presentations or publications.

All study findings and documents will be regarded as confidential. The IoR and study staff must not disclose such information without prior written approval from the Sponsor. Information about study participants will be kept confidential and managed according to the requirements of The Miriam Hospital's Institutional Review Board governing the protection of human subjects and the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA requirements are outlined in the Lifespan Informed Consent Form (ICF) Template, thus participant HIPAA authorizations are signed (or not) as part of the informed consent process.

11. Administrative Procedures

11.1 Critical Event Reporting

Critical events include the following classes of events: unanticipated problems involving risks to participants or others, suspension or termination of IRB approval, and suspected research misconduct.

Critical Events occurring at any time during conduct of the study will be reported to DAIDS and the Miriam Hospital IRB within one week of recognition.

11.2 Communicable Disease Reporting

Study staff members will comply with all local requirements to report communicable diseases, including chlamydia, gonorrhea, syphilis, and HIV, identified among study participants to the Rhode Island Health Department. Study investigators will include discussion of mandated reporting during the study informed consent process.

11.3 Access to HIV-Related Care

The investigators do not expect a screening population at high risk for HIV infection. However, should a study volunteer test reactive via the rapid HIV antibody screening test, the study clinician will refer him/her for additional counseling related to testing or diagnosis. Participants who do not have an identified primary care physician, and do not wish to be seen through the TMH Immunology Department, will be referred to the Rhode Island Health Department for follow-up testing and counseling.

11.4 Study Coordination

On site data management responsibilities will reside with the study staff at The Miriam Hospital under the supervision of the IoR or her designee. This will include managing and retaining prescreening data, STI/HIV/Pregnancy Results, Participant Enrollment and Completion Log; Demographic and Sexual/Product History Questionnaire CASI Database; USPE survey database; Audio Recordings and Transcripts/Summaries. The research team will maintain complete and accurate documentation for the study.

11.5 Study Discontinuation

NIAID, other government or regulatory authorities, or The Miriam Hospital Institutional Review Board may discontinue this study at any time. Ongoing safety monitoring will track the incidence of AEs and SAEs. In the event of an abnormal number of reported AEs and/or SAEs judged to be related to study product, or any other condition deemed as an emergency event by the study staff, the PSRT will direct the IoR to initiate a temporary hold on further enrollment. This study may also be discontinued for futility if the study is not fully enrolled after 12 months from initiation.

11.6 Approval of Study Protocol

The study protocol and/or other appropriate documents will be submitted to the IRB in accordance with local regulatory requirements prior to study initiation. All required approvals must be documented and communicated to the Sponsor before the first participant is enrolled in the study.

11.6.1 Amending the Protocol

Research staff should follow this protocol as written unless the Investigator or Study Clinician determines that immediate deviation is required to protect the rights and welfare of a participant. All protocol amendments will be submitted to the DAIDS MO, the DAIDS Regulatory Support Center, and the local IRB prior to the implementation of an amendment. At the DAIDS Medical Officer's discretion, submission to and approval by the DAIDS PSRC may also be required.

11.7 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, the protocol and the protocol informed consent form(s) will be approved, as appropriate, by The Miriam Hospital IRB and Western IRB. Upon receiving final approval from these IRBs and from DAIDS PSRC, all required protocol registration documents will be submitted to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) will not be reviewed or approved by the DAIDS PRO, and the site will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. The site will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification will be retained in the study's regulatory files.

Upon receiving final IRB approval(s) for an amendment, the research staff will implement the amendment immediately. An amendment registration packet will be submitted to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Again, study-specific ICF(s) will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification will be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

11.8 ClinicalTrials.gov

This protocol will be registered in *ClinicalTrials.gov* prior to study initiation.

12. Publication Policy

Publication and/or presentation of data derived from this study will follow applicable NIH publication policy, the publication policy for U19 AI101691, and the IPCP publication policy, and will occur only in agreement with the Principal Investigator and other Co-Investigators, as appropriate.

Each publication, press release, or other document that cites results from NIH grant-supported research will include an acknowledgment of NIH grant support and disclaimer such as, "The project described was supported by Award Number U19 AI101961 from the National Institute of Allergy And Infectious Diseases. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health."

Investigators will comply with the NIH Public Access Policy. This includes submission to PubMed Central (PMC), upon acceptance for publication, an electronic version of a final peer-reviewed manuscript resulting from research supported in whole or in part, with direct costs from National Institutes of Health. The author's final peer-reviewed manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process.

Investigators shall be free to use the results of the subject research for their own teaching, research, educational, clinical and publication purposes without the payment of royalties or other fees. The investigators agree to submit to ImQuest, Inc., for its review, a copy of any proposed publication resulting from the research at least thirty (30) days prior to submission, and if no response is received within thirty (30) days of the date submitted to ImQuest, Inc., it will be conclusively presumed that the publication may proceed without delay. If ImQuest, Inc., determines that the proposed publication contains patentable subject matters that require protection, ImQuest, Inc., may require the delay of the publication for a period of time not to exceed 60 days for the purpose of allowing the pursuit of such protection.

References

1. Skoler-Karpoff S, Ramjee G, Ahmed K, et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: A randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;372(9654):1977-1987.
2. Van Damme L, Govinden R, Mirembe FM, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *N Engl J Med.* Jul 31 2008;359(5):463-472.
3. Abdool Karim SS, Richardson BA, Ramjee G, et al. Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women. *AIDS.* Apr 24 2011;25(7):957-966.
4. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science.* 2010;329(5996):1168-1174.
5. CONRAD. HIV prevention study does not confirm pericoital tenofovir gel effectiveness - Protection observed in small group of women who used the product consistently [Press Release]. 2015; http://www.conrad.org/news-pressreleases-107.html. Accessed 4/9/15, 2015.
6. Morrow Guthrie K, Dunsiger S, Vargas S, et al. Perceptibility and the "Choice Experience": User Sensory Perceptions and Experiences Inform Vaginal Prevention Product Design. *Under Review.* 2015.
7. Carballo-Dieguez A, Dolezal C, Bauermeister JA, O'Brien W, Ventuneac A, Mayer K. Preference for gel over suppository as delivery vehicle for a rectal microbicide: results of a randomised, crossover acceptability trial among men who have sex with men. *Sex Transm Infect.* Nov 2008;84(6):483-487.
8. Carballo-Dieguez A, Exner T, Dolezal C, Pickard R, Lin P, Mayer KH. Rectal microbicide acceptability: results of a volume escalation trial. *Sexually Transmitted Diseases.* Apr 2007;34(4):224-229.
9. Ventuneac A, Carballo-Dieguez A, McGowan I, et al. Acceptability of UC781 gel as a rectal microbicide among HIV-uninfected women and men. *AIDS and Behavior.* 2010;14(3):618-628.
10. Bentley ME, Morrow KM, Fullem A, et al. Acceptability of a novel vaginal microbicide during a safety trial among low-risk women. *Fam Plann Perspect.* Jul-Aug 2000;32(4):184-188.
11. Morrow K, Rosen R, Richter L, et al. The acceptability of an investigational vaginal microbicide, PRO 2000 Gel, among women in a phase I clinical trial. *J Womens Health (Larchmt).* Sep 2003;12(7):655-666.
12. Rosen RK, Morrow KM, Carballo-Dieguez A, et al. Acceptability of tenofovir gel as a vaginal microbicide among women in a phase I trial: a mixed-methods study. *J Womens Health (Larchmt).* Apr 2008;17(3):383-392.
13. Fava JL, van den Berg JJ, Rosen RK, et al. Measuring self-efficacy to use vaginal microbicides: the Microbicide Use Self-Efficacy instrument. *Sex Health.* 2013;28(10).

14. Morrow KM, Fava JL, Rosen RK, Christensen AL, Vargas S, Barroso C. Willingness to use microbicides varies by race/ethnicity, experience with prevention products, and partner type. *Health Psychology.* 2007;26(6):777-786.
15. Morrow KM, Fava JL, Rosen RK, et al. Willingness to use microbicides is affected by the importance of product characteristics, use parameters, and protective properties. *Journal of Acquired Immune Deficiency Syndromes.* 2007;45(1):93-101.
16. Morrow KM, Fava JL, Severy L, et al. Contextualizing Microbicide Acceptability: Modeling Willingness to Use Vaginal Microbicides. in preparation.
17. Morrow KM, Rosen RK, Salomon L, et al. Using integrated mixed methods to develop behavioral measures of factors associated with microbicide acceptability. *Qualitative Health Research.* 2011;21(7):987-999.
18. Vargas S, Fava J, Severy L, et al. Psychometric properties and validity of a multi-dimensional risk perception scale developed in the context of a microbicide acceptability study. *Archives of Sexual Behavior.* Forthcoming, 2016.
19. Morrow KM, Rosen, R.K., Mayer, K.H., Maslankowski, L., and El-Sadr, W.M. The effect of formulation factors on vaginal microbicide acceptability: A meta-analysis of qualitative data from three Phase I clinical trials in the United States. *Microbicides 2006 Conference*. Cape Town, South Africa2006.
20. Morrow KM. Microbicide Formulations and Delivery Systems: Behavioral Perspectives [Invited Keynote Address]. *Microbicides 2008 Conference*. New Delhi, India2008.
21. Morrow K, Dunsiger S, Fava J, et al. Which user experiences potentiate adherence to vaginal microbicides?: What user characteristics predict product experience, and which experiences predict use? [poster]. Paper presented at: XIX International AIDS Conference (AIDS 2012)2012 Washington, D.C., USA.
22. Morrow KM, Fava JF, Katz D, et al. User sensory perceptions and experiences of vaginal gels correspond to gel properties and performance: The impact on willingness to use. Paper presented at: Oral Presentation at 2012 International Microbicides Conference2012; Sydney, Australia.
23. Morrow KM, Fava JL, Rosen RK, et al. Designing preclinical perceptibility measures to evaluate topical vaginal gel formulations: relating user sensory perceptions and experiences to formulation properties. *AIDS Res Hum Retroviruses.* Jan 2014;30(1):78-91.
24. Morrow K, Rosen R, Vargas S, et al. More…? Less…? Just right…? The Role of Perceived Volume in Gel and Film Perceptibility During Intercourse, and its Impact on Product Preference. *International HIV R4P (Research for Prevention) Conference*. Cape Town, South Africa2014.
25. Morrow K, Rohan L, Rosen R, et al. Vaginal Film User Evaluations: Developer Considerations from Initial Impressions and User Sensory Perceptions and Experiences during Vaginal Sex. *International HIV R4P (Research for Prevention) Conference*. Cape Town, South Africa2014.
26. Tien D, Schnaare RL, Kang F, et al. In vitro and in vivo characterization of a potential universal placebo designed for use in vaginal microbicide clinical trials. *AIDS Research and Human Retroviruses.* Oct 2005;21(10):845-853.

27. Mahalingam A, Simmons AP, Ugaonkar SR, et al. Vaginal microbicide gel for delivery of IQP-0528, a pyrimidinedione analog with a dual mechanism of action against HIV-1. *Antimicrob Agents Chemother.* Apr 2011;55(4):1650-1660.
28. Dezzutti CS, Rohan LC, Wang L, et al. Reformulated tenofovir gel for use as a dual compartment microbicide. *Journal of Antimicrobial Chemotherapy.* 2012;67(9):2139-2142.
29. Anton PA, Saunders T, Elliott J, et al. First phase 1 double-blind, placebo-controlled, randomized rectal microbicide trial using UC781 gel with a novel index of ex vivo efficacy. *PLoS One.* 2011;6(9):e23243.
30. Javanbakht M, Murphy R, Gorbach P, LeBlanc MA, Pickett J. Preference and practices relating to lubricant use during anal intercourse: Implications for rectal microbicides. *Sexual Health.* 2010;7(2):193-198.
31. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *New England Journal of Medicine.* 2015;372(6):509-518.
32. Fowler J, F.J. *Survey Research Methods, Third Edition*. Thousand Oaks, CA: Sage Publications; 2002.
33. Guest G, MacQueen KM, Namey EE. *Applied thematic analysis*: Sage; 2011.
34. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
35. Kaufman C, Venkatapathy R. *Windows Azure Security Overview*: Microsoft;2010.

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