Project Brief: Trial to Assess Acceptability and Safety of Two Placebo Prototype Vaginal Films

Full Title of Study/Programme	Trial to Assess Acceptability and Safety of Two Placebo Prototype Vaginal Films **Short Title:** MATRIX-002
Technical Focus Area/Key Words	Two-arm, randomized, multi-center trial of monthly vaginal administration of two placebo prototype films
Rationale	Topical microbicides are agents designed to prevent or at least substantially reduce the risk of sexual acquisition and transmission of HIV when applied to the genital or rectal mucosa. Vaginal films are an attractive dosing option for topical (vaginal) delivery of anti-HIV drugs. In terms of costs of production and manufacturing, films are relatively inexpensive, scalable, physically and chemically stable, and amenable to a range of active ingredients including combinations of excipients. In terms of use, films are discreet, portable, and easy to store. Vaginal films can deliver fixed doses of pharmacologically active agents with minimal mess or leakage and without an applicator. Due to their small volume, films also generate no significant alterations in innate microbiome as shown in previous clinical evaluation for our FAME program (U19 AI0826391, U19 AI1202492), and incur less dilution of endogenous antiviral or antibacterial properties in vaginal fluids as compared to vaginal gels. Feedback from women in several clinical and focus-group studies – NCT01231763 (FACE)3, NCT02908503 (FLAG)4, NCT02602366 (Quatro)5, PASII6, NCT01334827 (MIST)7,8, NCT01548560 (FAME 02)9, FAME 02B10, NCT02579083 (VAST)11, NCT01989663 (FAME 04)12, NCT02280109 (FAME 05)13, NCT03537092 (FAME 101)14, FAME 102 (unpublished data), NCT04319718 (FAME 103)15, NCT04391036 (FAME 103B)16 – supported the willingness for women to use such products and the advancement and development of vaginal films for discrete HIV prevention.5,6,9-11 The long-term goal of the VALUE (Vaginal film as A Low-cost, User-administered, and Extended-release product) project is to develop and evaluate an extended-release vaginal film containing dapivirine, a potent NNRTI, which could provide protection from HIV for at least one month following a single application. Previously, the Pitt/MWRIF team developed and evaluated quick dissolve films for on-demand vaginal administration of several anti-HIV drug candidates including dapivirine.9,10,12,13 We have also confirmed the feasibility of design of a monthly film platform (LATCH R61/33 AI142687)17 in a nonhuman primate (macaque) model. Furthermore, retention of films within the vagina was established during menses and sex in the macaque model. The VALUE project aims to design a one-month vaginal film containing dapivirine as the active pharmaceutical ingredient (API) to provide a low cost and convenient option for women for protection from HIV infection through sex. Previous

	studies have supported the acceptability and safety of the quick dissolve and 7-day sustained release films, but there is limited data regarding a monthly vaginal film. MATRIX-002 is a randomized trial assessing the acceptability and safety of two vaginal placebo film products that differ in shape. Specifically, the 2"x2" films differ with respect to shape of the corners. One film product is square in shape, while the second product has rounded edges on all four corners. These differences may impact product acceptability and usability. The proposed study will evaluate the acceptability, safety, and self-insertion success of these 1-month placebo film products when applied vaginally with and without sex at five clinical sites, one in the United States and four in South Africa, Zimbabwe, and Kenya. Building on the existing evidence base for the quick dissolve and 7-day extended-release films, multiple African sites will participate in MATRIX-002 alongside the US site, affording the opportunity to obtain critical information and feedback from women who have the greatest potential to benefit from access to a range of HIV prevention products. This study of the one-month placebo vaginal film will examine overall satisfaction with the film after using it, multiple components and correlates of acceptability, as well as topics relevant to adherence and preference. The design of these assessments is informed by a recent systematic review of the Theoretical Framework of Acceptability (Sekhon),18 published by Ortblad et al.19 Additionally, by investigating the attitudes and experiences that sexual partners had while MATRIX-002 participants used the vaginal film, this study hopes to gain a deeper understanding of how partners' opposition or support may affect a user's ability to safely, correctly and consistently use a vaginal film for HIV prevention in the future. This, in turn, can contribute to efforts to mitigate concerns and cultivate support among men for HIV prevention research, HIV prevention products, and microbicide use. Data from in-depth interviews (IDI) may also provide insight to the strategies and counseling messages that could be used in couples' education and counseling for future trials, with the objective of promoting use of the vaginal film.
Primary Objectives	**Acceptability** • Participant ratings of overall satisfaction with use of the placebo vaginal films.
Secondary Objectives	**Safety** • To assess the safety of two placebo film types (A and B) when administered vaginally once monthly for two months. **Usability** • To assess participants' ability to properly insert the placebo vaginal film.
Tertiary/Exploratory Objectives	**Participant acceptability, attitudes and experiences** • To explore multiple dimensions of acceptability of two placebo film

	types (A and B) and participants' attitudes towards and experiences with the vaginal film. **Sexual partner attitudes and experiences** • To explore sexual partners' attitudes towards and experiences with the vaginal film. **Vaginal microenvironment** • To assess the impact of placebo film use on participants' vaginal microenvironment when administered vaginally once monthly for two months. **Social harms and social benefits** • To describe the reported experiences of social harms and social benefits over the course of vaginal film use.
Primary Endpoints/Outcomes	**Acceptability** • Participant ratings of overall satisfaction with use of the placebo vaginal films.
Secondary Endpoints/Outcomes	**Safety** • Proportion of participants with genitourinary Grade 2 or higher Adverse Events deemed related to study product. **Usability** • Proportion of participants with clinically assessed proper insertion (more than half of the vaginal film proximal to introitus).
Tertiary Endpoints/Outcomes	**Participant acceptability, attitudes and experiences** • Participant responses to quantitative acceptability assessments and IDI questions. Multiple dimensions will be explored, including: o Vaginal film attributes, including acceptability (e.g., ease of insertion, burden, perceived effectiveness of film as delivery form) and preferences o Experience and comfort with inserted vaginal film (e.g., expulsions, leakage, awareness of film during daily activities) o Experience during sex and menses o Vaginal practices and concomitant vaginal product use while using vaginal film o Perception of sexual partners' attitudes towards vaginal film o Perceived benefits and concerns/challenges with the vaginal film as a future HIV prevention option o Interest in using vaginal film as a future HIV prevention option **Sexual partner attitudes and experiences** • Sexual partner responses during IDI related to: o Vaginal film attributes, including acceptability and preferences • Perception of participant's experience using the vaginal film during the study • Physical sensation of the participant's vaginal film use during sex (as relevant) • Perceived benefits and concerns/challenges with the vaginal film as a future HIV prevention option **Vaginal microenvironment** • Change from baseline in vaginal pH following film use during the two study phases (i.e., with and without sexual abstinence requirement).

	• Change from baseline in quantity of selected vaginal microbiota following film use during the two study phases (i.e., with and without sexual abstinence requirement). • Change from baseline in Nugent score following film use during the two study phases (i.e., with and without sexual abstinence requirement). **Social harms and social benefits** • Participant self-report of social harms (i.e., non-clinical adverse consequences of study participation or product use that may manifest in social, psychological or physical ways). • Participant or sexual partner self-report of social benefits (e.g., positive consequences of product use disclosure, self-confidence, improved communication with intimate partner) resulting from vaginal film use and/or study participation.
Study Design	Two-arm, randomized, multi-center trial of monthly vaginal administration of two placebo prototype films
Study arms	N/A
Study population	HIV seronegative adult (18-45 years old) persons assigned female sex at birth who are at low risk of acquiring HIV infection (henceforth referred to as "participants"), and sexual partners of evaluable participants (henceforth referred to as "sexual partners")
Study sample size (within five sites)	MATRIX-002 will enroll approximately 100 evaluable participants and a subset of up to 30 sexual partners of evaluable participants for in-depth interviews (IDI)
Follow up/duration	Approximately nine weeks of follow-up per participant is planned with a projected accrual period of approximately 3-6 months
Study/Programme sites	Five sites in the US and sub-Saharan Africa (SSA): 1. University of Pittsburgh (Pitt)/Magee-Women's Research Institute and Foundation (MWRIF) clinical research site (CRS); 2. Aurum Institute CRS; 3. Harare Health and Research Consortium (HHRC) CRS; 4. Wits Reproductive Health and HIV Institute (Wits RHI) CRS; 5. Kenya Medical Research Institute (KEMRI) CRS
Study/Programme duration	The total duration of the study will be approximately 6-9 months
Intervention	Two-arm, randomized, multi-center trial of monthly vaginal administration of two placebo prototype films
Operations	Data and Specimen Collection
Investigators	**Wits Reproductive Health and HIV Institute (Wits RHI)** Prof Thesla Palanee-Phillips (Site Investigator) Dr Nkosiphile Ndlovu (Site Investigator of Record)
Other Partners & Collaborators	Clinical Research Sites: 1. University of Pittsburgh (Pitt)/Magee-Women's Research Institute and Foundation (MWRIF) CRS 2. Harare Health and Research Consortium (HHRC) CRS 3. The Aurum Institute CRS 4. Kenya Medical Research Institute (KEMRI) CRS MATRIX USAID

	Pitt / MWRIF
Progress Update	The study activation was on 14 March 2024 and the site screened the first participant on 18 March 2024. There are no randomised participants to date.
Frequency of donor narrative report	n/a
Overall Study/Project Contact	Dr Nkosiphile Ndlovu,
Briefing owner and date	Sihle KaPhila Zulu, 03 April 2024