MTN-045

Dual Purpose Prevention (DPP) Product Preferences among Couples

Microbicide Trials Network

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LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ARV	antiretroviral
ART	antiretroviral therapy
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
BRWG	Behavioral Research Working Group
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAB	community advisory board
CFR	Code of Federal Regulations
CRF	case report form
CMRB	Clinical Microbicide Research Branch
CRS	clinical research site
CWG	Community Working Group
DAIDS	Division of AIDS
DCE	discrete choice experiment
DPP	dual purpose prevention
DPV	dapivirine
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
FTP	File Transfer Protocol
GCP	Good Clinical Practices
HHS	Health and Human Services (US)
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICRC	International Clinical Research Center
IDI	in-depth interview
IEC	Independent Ethics Committee
IND	investigational new drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IPV	intimate partner violence
IRB	Institutional Review Board
LNG	levonorgestrel
LOC	Leadership and Operations Center
MTN	Microbicide Trials Network
MO	Medical Officer
MU-JHU	Makerere University – Johns Hopkins University
MPT	multi-purpose prevention technology
NIH	National Institutes of Health
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
OHRP	Office for Human Research Protections
PMTCT	prevention of mother to child transmission

PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PTID	Participant Identification
QC	quality control
QDMC	Qualitative Data Management Center
RE	regulatory entity
RPL	random parameters logit
RSC	Regulatory Support Center
RTI	Research Triangle Institute
SMC	Study Monitoring Committee
SOP	standard operating procedure
SRH	sexual and reproductive health
SSA	sub-Saharan Africa
SSP	study specific procedures
STI	sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
UPMC	University of Pittsburgh Medical Center
US	United States
UZCHS	University of Zimbabwe College of Health Sciences
UZ-UCSF	University of Zimbabwe – University of California, San Francisco
VCF	vaginal contraceptive film
VR	vaginal ring
VOICE	Vaginal + Oral Interventions to Control the Epidemic

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INVESTIGATOR SIGNATURE FORM

Version 1.0; February 25, 2019

A Study of the Microbicide Trials Network

Funded by:
Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health (NIH)

IND Sponsor:
A Non-IND Study (DAIDS Protocol ID: 38598)

I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); standards of the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (E6); Institutional Review Board (IRB)/Independent Ethics Committee (IEC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain MTN study records in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC policies and procedures. Study records must be maintained on-site for the entire implementation period of the study and a minimum of at least three years after completion of research as per 45 CFR 46.115 (b). DAIDS/designee will inform the investigator/institution as to when these documents no longer need to be retained.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record (print)

_____ _____
Signature of Investigator of Record Date

MTN-045

Dual Purpose Prevention (DPP) Product Preferences among Couples

PROTOCOL SUMMARY

Short Title:	Couple User Preferences in Dual purpose prevention products (CUPID)
Funders:	Division of AIDS, NIAID, NIMH, NICHD, US NIH
Protocol Chair:	Alexandra Minnis, PhD
Protocol Co-Chair:	Juliane Etima, MA Psy
Sample Size:	Approximately 400 couples
Study Population:	Heterosexual couples who have been in a relationship for ≥ 3 months (living together or not) and are interested in contraception and/or HIV prevention.
Study Sites:	Site(s) in sub-Saharan Africa as designated by the MTN Executive Committee.
Study Design:	Cross-sectional study that will utilize questionnaires, including Discrete-Choice Experiments (DCE) and joint decision tasks, to assess couples' preferences related to dual purpose prevention (DPP) products that could be used to prevent unintended pregnancies and HIV infection. Post-survey explanatory in-depth interviews (IDIs) will be conducted with a subset of participants.
Study Duration:	Approximately 12-15 months for recruitment and enrollment at each site.

Primary Objectives:

- To determine heterosexual couples' preferences for a DPP product to inform product delivery and future product design to maximize uptake and willingness to use among sub-Saharan African heterosexual couples.

- To assess the level of influence of the male partner on a woman's preferences for a DPP product and on her decision-making process regarding product preferences and use.

Primary Endpoints:

- Attributes of a DPP product that influence preferences among heterosexual couples.

- Differences in DPP product attribute preferences when comparing individual to couples' choices (e.g., woman's individual preferences vs. preferences indicated through the joint couples decision task).

Secondary Objectives:

- To identify factors that may influence DPP product interest and preferences in heterosexual men, women and couples, including individual and relationship characteristics, and product "positioning" (i.e., contraceptive+HIV prevention vs. HIV prevention+contraceptive).

- To examine differences in preferences and individual vs. joint decision-making by several sociodemographic factors, including age of the woman (e.g., 18-24 vs. 25-40) and parity (nulliparous vs. parous).

Secondary Endpoints:

- Salient relationship-based and decision-making factors that influence DPP product interest and preferences.

- Differences in attributes salient to preferences by sociodemographic factors such as age and parity that may reflect lifecourse stage.

Exploratory Objectives:

- To explore relationship dynamics and their influences on the decision-making process for individuals and couples.

- To explore the extent to which male partner interest for, or acceptance of, a DPP product influences the female partner's willingness to use the product.

- To estimate uptake of a range of potential DPP products that can be incorporated in cost-effectiveness modelling of future products.

Exploratory Endpoints:

- Salient relationship characteristics, norms and communication factors that influenced participants' decision-making process.

- Differences in product preferences, when comparing individual to couples' choices, that characterize the male partner's role in females' preferences.

- Likelihood of using each DPP product, overall and by subgroup, as estimated through analysis of DCE data.

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Dual Purpose Prevention (DPP) Product Preferences among Couples
Protocol Number:	MTN-045
Date:	February 25, 2019

1.2 Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 Microbicides, Human Immunodeficiency Virus (HIV) Prevention and Contraception

In 2016, 36.7 million people globally were living with the human immunodeficiency virus (HIV). In the same year, 1.8 million people were newly infected and 1 million lost their lives to HIV-related illnesses.[1] The burden of the HIV/AIDS epidemic is particularly high in sub-Saharan Africa (SSA) where 70% (approximately 25.5 million) of all HIV-infected people live and where 1.4 million new infections occurred in 2015.[2] Heterosexual vaginal intercourse remains the major mode of HIV transmission in SSA, with women bearing the greatest impact of the epidemic. Every 60 seconds, a young woman is infected with HIV[3] and women account for approximately 51% of people living with HIV worldwide.[1] Globally, HIV/AIDS remains the leading cause of death among women of reproductive age (15 to 44 years of age), and among adolescent girls in Africa.[4] The ongoing development of safe and effective HIV prevention technologies easily accessible to under-resourced communities and countries remains a public health priority.

Unprotected heterosexual intercourse is the leading mode of HIV acquisition among women. Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition. However, women may be unable to negotiate condom use with their partners, or couples may be unwilling to use condoms for other reasons. Although developing discreet, female-controlled methods of HIV prevention remains a global concern, many women choose to discuss HIV prevention with their partner(s). Thus, developing HIV prevention options that meet the needs of couples is also an urgent priority.

Although oral pre-exposure prophylaxis (PrEP) holds great promise for HIV prevention, its scale and coverage remain limited outside the United States (US). The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 60,000 people were taking oral PrEP in 2016, with most of them in the US, though this estimate does not include those who access PrEP through less regulated channels like the Internet. In Africa, UNAIDS identified several barriers to scaling up PrEP use, including cost, limited awareness, limited regulatory approval (approved in only seven countries worldwide as of 2017), and limited availability of both PrEP and the ancillary clinical services needed to support its successful implementation.[5]

While generally effective for use as oral PrEP, Truvada tablets require a daily dosage schedule to maintain protective levels over time.[6,7] Also, while Truvada is generally safe for use as oral PrEP, systemic delivery of a drug increases the risk and severity of its possible side effects relative to more localized drug delivery alternatives like microbicides. Lastly, behaviorally and conceptually linking the taking of pills (a daily prevention strategy) with sexual activity (an episodic occurrence) could be difficult for those who would find a pericoital prevention strategy more feasible and/or preferable. Therefore, even if readily available to everyone, the product characteristics of daily oral PrEP present acceptability and adherence challenges. Furthermore, it does not address other infections that can still be passed via condomless sex.

In addition to HIV acquisition, unintended pregnancies exert a health and economic burden in the developed and developing world. Globally, nearly half of pregnancies (100+ million per year) are unintended.[8] On average, women in developing countries have many more pregnancies than women in developed countries, and their lifetime risk of death due to pregnancy is higher.[9] Developing regions accounted for approximately 99% of the global maternal deaths in 2015, with SSA alone accounting for roughly 66% and almost one third occurring in South Asia.[10] Many highly effective contraceptives have been available for decades. Low utilization rates and high discontinuation rates remain problems due to factors including inconvenience, cost,

inaccessibility, and a constrained ability for women in many developing nations to fully participate in sexual and reproductive decision-making.[11]

In developing countries, the number of women who would like to avoid pregnancy but are not using a modern contraceptive method (i.e., unmet need for family planning)_is estimated at 215 million women.[12] This roughly translates to a quarter of all reproductive-age women who want to avoid pregnancy, and accounts for over 80% of all unintended pregnancies in developing countries.[12] Though declining, fertility rates, unmet need for family planning and unintended pregnancy rates are highest in SSA, where it is estimated that 4.8 children are born to every woman, 28% of married women aged 15-49 do not use modern contraceptive methods, and 86 unintended pregnancies per 1000 women occur annually.[13,14] These figures are higher in Uganda (5.6 children born to every woman, 33% unmet need for family planning, and more than 1.2 million unintended pregnancies occur annually) and lower in Zimbabwe (3.8 children born to every woman, 9.9% unmet need for family planning, and about 300,000 unintended pregnancies occur annually), the two countries taking part in this study.[14,15]

Unintended pregnancy leads to underuse of antenatal care, and is a major contributor to maternal and infant morbidity and mortality. The Guttmacher Institute estimated that if all unmet need for family planning was eliminated, the number of unintended pregnancies in developing countries per year would be reduced by three quarters, leading to 23 million fewer unplanned births, 36 million fewer induced abortions, and 76,000 fewer maternal deaths.[13,16] In addition to improved sexual and reproductive health outcomes, contraceptive use increases women's opportunities for educational and economic achievements and improved trajectories throughout the life course. The United Nations 2030 Agenda for Sustainable Development articulates goals to "ensure healthy lives and promote well-being for all at all ages" and "achieve gender equality and empower all women and girls", and it lists access to sexual and reproductive health services as a key strategy to achieving both of these goals.[17]

Lastly, pregnant and breastfeeding women in areas with high HIV incidence rates, particularly in SSA, are at high risk of acquiring HIV.[18] Biological factors during pregnancy and breastfeeding increase susceptibility to HIV infection, while social and behavioral factors during pregnancy and breastfeeding may increase exposure to HIV infection.[19] Given the linkages between pregnancy prevention and HIV prevention, it would be logical to expand women's sexual and reproductive decision-making choices and combine these two components of women's sexual and reproductive health. To this end, research is under way to develop highly acceptable, effective, affordable, dual-purpose contraceptive and HIV prevention options.

Multipurpose prevention technologies (MPTs), often referred to as "combination" or "dual" technologies, are innovative products currently under development that are designed for at least two sexual and reproductive health (SRH) prevention indications. These products are intended to simultaneously prevent unintended pregnancy and sexually transmitted infections (STIs), including HIV.[20] MPTs include vaccines, contraceptives, microbicides and devices such as intravaginal rings and diaphragms. Barrier devices like male and female condoms and diaphragms are already available, and research is underway to develop new and more innovative biomedical interventions that may allow women and young girls to address multiple SRH issues with one product. The majority of new MPT candidates in development focus on the development or improvement of physical barriers, chemical barriers, and physical/chemical barrier combinations.[20] MPTs potentially offer a cost-effective approach to addressing an important public health need, which could result in social and economic benefits to women and their families worldwide.

Drug delivery forms like vaginal rings (VRs), vaginal inserts, vaginal films, and oral tablets can be designed for various dual purpose prevention (DPP) indications. For example, VRs could be loaded with both HIV prevention and contraception medications, like the dapivirine-levonorgestrel ring being developed by the International Partnership for Microbicides (IPM) and currently being evaluated in MTN-044/IPM 053/CCN019. Furthermore, DPP products like the dapivirine-levonorgestrel VR can be designed with higher drug loading doses to allow less frequent administration, which may reduce user and provider burden, streamline follow-up, and improve adherence.

It is important to develop a range of HIV prevention products that can serve as viable alternatives and/or complements to consistent condom use and oral PrEP, including formulations able to deliver multiple drugs (e.g., anti-HIV-1 and hormonal contraception) in combination. However, as past PrEP and microbicide studies have shown, drug efficacy does not translate to drug effectiveness when people do not use the product as intended.[21-23] Threrefore, it is crucial for products to be designed so that they can not only deliver enough drug to block HIV transmission or fertilization, but are also a good behavioral fit with the product's intended end-users. To achieve this, women need a range of prevention choices that can cater to all lifestyles and all lifecourse stages.

MTN-045 is a cross-sectional behavioral study conducted by the Microbicide Trials Network (MTN) to evaluate user preferences related to DPP product use. This study will assess couples' preferences for various DPP product attributes as well as how socio-cultural norms and relationship dynamics might influence those preferences.

2.2 Description of Potential DPP Product Delivery Forms

Adherence to a product is required to determine why a product may or may not be effective. It is unknown what level of participant adherence is needed in order to achieve sufficient levels of drug to provide efficacy. Even with adherence levels as high as 60%, the effectiveness of a product can be reduced to less than half of its true biological efficacy,[24] making it difficult to determine whether lack of effectiveness is due to inefficacy of the drug or simply lack of use by participants.[25]

It is essential that DPP products are used correctly and consistently, and importantly, are acceptable to the user. For example, a product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse, while an on-demand product might be more acceptable and less burdensome to use for women with infrequent sexual activity. It is likely that products that fit women's lifestyles will be more acceptable and achieve better adherence than products that do not, and that better adherence to a product will translate into higher effectiveness of the product.

The core products evaluated in this study may include the following four drug delivery forms: VRs, vaginal inserts, vaginal films, and oral tablets. Injectables were not included as a potential product choice because the focus of this study is on drug delivery forms currently in the MPT pipeline.[26] Although there are additional MPT delivery forms in the research and development pipeline, including gels and barrier devices, we limited the number of delivery forms to the above four for two reasons: ensure sufficient statistical power to detect preference differences; and prioritize delivery forms where end-user input could best inform product development, clinical research and eventual roll-out of effective products. We selected products that vary in duration of effectiveness and use characteristics (e.g., on demand, daily, weekly, monthly or longer).

2.2.1 Vaginal rings

Multiple clinical trials have evaluated acceptability of and adherence to an HIV prevention VR, the dapivirine (DPV) VR, among reproductive-aged women in Africa and the US.[27-31] Self-reported adherence to VR use was very high overall, with >80% of participants across studies saying they used the VR every day. Blood plasma drug levels supported these findings, although subgroup analyses of residual DPV concentrations in used VRs suggest that the majority of women inconsistently used the VR throughout their participation in ASPIRE.[27]

The most commonly stated activities that led to voluntary removal of the DPV VR were cleaning, menses and sexual intercourse, while the most commonly stated activities that led to involuntary expulsions of the VR were urination/defecation and sexual activity. Reasons for removing the VR included: male partner's wishes, menses, and perceived side effects. In ASPIRE, drug detection appeared to increase after the first months of VR use and become stable after the first year, which may indicate that some time was needed for participants to become comfortable with the VR.

Self-reported acceptability of the DPV VR was high across DPV VR studies, with most study participants saying the ring was comfortable, easy to use, did not interfere with daily activities, and that they would be willing to use the VR if shown to be effective for HIV prevention.[32-34] A subset of ASPIRE[35] study participants selected for qualitative interviews (214 women across multiple sites in Uganda, Malawi, Zimbabwe and South Africa) reported similarly favorable opinions about the VR: ease of ring insertion, lack of interference during daily activities, discreetness, color and feel of the VR, and inability to feel the ring when properly positioned. Although many ASPIRE interview respondents expressed initial fears and concerns that the VR was too big, that it would fall out, that it would harm the vagina, or that it would be felt during sex by their partner, most overcame these fears after using the VR. Instances of physical discomfort occurred mostly during the first months of use, and were usually attributed to improper insertion.

VRs containing contraceptives have been in development for over forty years, with two achieving marketing approval: a monthly ring delivering a combination of etonogestrel and ethinyl estradiol, more commonly known as NuvaRing®, and a three-month ring geared towards breastfeeding women that delivers progesterone alone, more commonly known as Progering®.[36,37] A third VR was approved for use in 2018, a yearly ring delivering a combination of segesterone acetate and ethinyl estradiol, more commonly known as Annoverra™.[38]

Combination contraceptive VRs like NuvaRing and Annoverra are less user-dependent and allow their users to exert better control over their menstrual bleeding than oral contraceptives, enhancing the rings' adherence and acceptability profiles. Similar to the DPV VR, most participants in contraceptive ring studies were satisfied with the ring, felt the ring was easy to use, rarely felt the ring during sex or during daily activities, became more comfortable with and less concerned about ring use over time, did not perceive side effects, and would recommend the ring to others.[39-42] In one study in Rwanda[39], sexual comfort played a significant role in ring acceptability of the participants and their partners, suggesting cultural norms around sexuality can be a positive influence. Also similar to the DPV VR, the most common reasons for ring removal were washing, sexual intercourse and difficulty with VR insertion.

2.2.2 Oral tablets

Multiple clinical trials have evaluated acceptability of and adherence to an HIV prevention oral tablet, the Truvada oral tablet, among reproductive-aged women in Africa.[27,43-51] Overall, Truvada tablet adherence tended to be high by self-report (>88% across studies) and returned pill counts

(>75% across studies), but less consistently so by blood plasma drug levels (from <30% in VOICE to 86% in the Partners Demonstration Project). Most VOICE and FEM-PrEP study participants did not use the study products daily, and lower adherence was associated with characteristics that predicted a higher risk of HIV acquisition. However, those results markedly differed from Partners PrEP study results which displayed a significant reduction in risk of HIV-1 acquisition. Of note was that VOICE participants who were most likely to adhere were similar in terms of age and marital status to women in the Partners PrEP study.

Barriers and facilitators to adherence were assessed in the HPTN 067 and FEM-PrEP studies. Facilitators included: participant support for the research, HIV risk reduction, personal experiences with persons living with HIV/AIDS, strategies and tools such as adherence counseling and reminder alerts, social and emotional support (e.g., from partners and clinic staff), material support (e.g., financial reimbursement and clinical care). Barriers included: concerns about side effects, community stigma and distrust, privacy concerns (e.g., disclosure to partner, being identified as an HIV positive person), negative clinic or research participation experiences, and Truvada tablet characteristics (e.g., odor, size). Lastly, data from Partners PrEP and other Phase 3 PrEP studies like iPrEx and VOICE indicate that adherence at early time points predict adherence over the next one to two years. One study, HPTN 067, found acceptability could be enhanced by interpersonal support, personal belief in PrEP's efficacy, cellphone and other reminders, and keeping pills at hand, and that a daily dosing regimen may lead to better habit formation and more forgiveness for missed doses.

Oral tablets containing contraceptives, commonly called birth control pills, have been in the market for over 50 years, and are one of the most widely prescribed and available forms of contraception in the world.[52] Unlike VRs, oral contraceptives must be taken every day to be effective, can be started any day of the menstrual cycle, and have additional prescribing limitations. When used every day and as indicated, birth control pills are highly effective (0.3% failure rate over the first year of use). However, actual first-year failure rates are typically around 9% due to product discontinuation or poor adherence. It is estimated that 40% of oral contraceptive users miss more than one pill per month, and more than half of users missed taking their pills at least once in the last year, with 20% of those not taking their pills during a time of high pregnancy risk. Furthermore, breakthrough bleeding caused by non-perfect adherence may contribute to one third of women discontinuing oral contraceptive use in the first year of use.

The most common reasons for contraceptive failure are missed doses, extending the "rest" period beyond seven days, vomiting or diarrhea, and drug interactions. The most common reasons for non-adherence to and discontinuation of oral contraceptives during the first year of use are side effects (including breakthrough bleeding, breast tenderness, bloating and nausea), lack of access, and confusion with product instructions.

2.2.3 Vaginal inserts

Rapidly disintegrating topical inserts offer many advantages as on-demand drug dosage forms: inexpensive, portable, easy to apply, discreet, user-initiated, and suitable for vaginal application. Vaginal inserts usually take the form of vaginal suppositories, tablets or capsules, and usually are inserted into the vagina using a plastic applicator.[53] There are no vaginal inserts approved to deliver topical HIV prevention medication at this time. See Section 2.5 for a summary of data from studies evaluating women's preferences for hypothetical HIV prevention vaginal inserts.

Vaginal inserts currently in the market are typically used to deliver: spermicides for fast-acting contraception; antifungal medications to treat yeast infections; or, a variety of hormones to

supplement fertility treatments, induce labor, or relieve vaginal dryness and other sexual symptoms of menopause.[53]

Vaginal inserts are generally considered both safe and effective, and may provide faster and more targeted relief when treating yeast infections and vaginal dryness than oral medications, along with fewer side effects.[53,54] Vaginal inserts for contraception tend to be less effective than more common methods of birth control. According to Planned Parenthood[55], 18 percent of women using contraceptive suppositories as their sole method of contraception will become pregnant each year despite using them correctly. With imperfect use, this figure can be as high as 28 percent. It is possible this is because enough time has to pass after insertion to allow the medication to melt and the spermicide to disperse.

2.2.4 Vaginal films

Vaginal films offer similar advantages as on-demand drug dosage forms as vaginal inserts, including portability, ease of use, and discreetness. Vaginal films are typically small, thin, water-soluble sheets similar to wax paper that can be inserted into the vagina without an applicator.[56] Researchers have been developing vaginal films to deliver topical HIV prevention medication for years, but none are approved for use at this time. See Section 2.5 for a summary of data from studies evaluating women's preferences for hypothetical HIV prevention drug delivery forms, including vaginal films.

Vaginal films currently in the market are used most commonly to deliver hormone-free spermicidal contraceptives, and are typically available over-the-counter.[56] Vaginal contraceptive film (VCF) must be manually inserted at least 15 minutes before intercourse and far enough inside the vagina to be in contact with the cervix, in order to be effective for up to three hours after insertion.

VCF is considered to be an effective and safe contraceptive when used consistently and as indicated. According to Apothecus Pharmaceutical[57], the manufacturer of VCF, only 2 percent of VCF users have reported minor irritation or burning of the vagina or penis. The manufacturer also maintains that across the many safety and efficacy studies conducted worldwide, VCF has a 94 percent success rate when used as directed (i.e., only 5.9 out of 100 women who use VCF for one year will get pregnant).

However, it is estimated that 26 out of every 100 VCF users would become pregnant during the first year, similar to the failure rate of all spermicidal methods, which is at 28 out of 100 women with typical, "imperfect" use.[56,58] Furthermore, research suggests that frequent use of spermicidal products containing nonoxynol-9 can increase vaginal irritation, which may increase the risk of getting STIs from infected partners, including HIV.[59]

2.3 Motivations for Product Use

2.3.1 HIV prevention

Participant adherence to HIV prevention products tended to be lower than anticipated in many of the studies described in Sections 2.2.1 and 2.2.2. One possible factor that may contribute to low adherence is participants' varying perceptions of HIV risk. A woman's perception of HIV risk is influenced by her individual level behaviors, such as engagement in high-risk sex, as well as the social-cultural context in which she lives. This perception of risk has often been linked to willingness to participate in hypothetical HIV prevention trials[60-71] and occasionally to interest in and acceptance of an HIV prevention method.[72]

Despite these linkages, the question remains: how does one's perception of HIV risk contribute to product adherence? One might expect that a higher perception of risk would lead to more consistent product use due to a greater desire for protection. However, a study in India found that contrary to this hypothesis, increased HIV risk perception was negatively associated with consistent gel use. Indeed, women who perceive themselves at higher risk may be less able to adhere to product use for a host of contextual reasons.[73]

Further, it is not well understood how regular (e.g., monthly) HIV testing conducted in the context of most HIV prevention clinical trials may change individual risk perception and adherence behavior over time. Other motivations for joining an HIV prevention trial, such as increased access to quality health care and altruism, may also contribute to product adherence. Lastly, participants in randomized, placebo-controlled trials may be less motivated to use study product when they do not know if they are using the active medication, or when the effectiveness of the active medication has not been established.

2.3.2 Contraception

Women's reasons for using contraception and for choosing among contraception methods vary depending on many factors, including lifecourse stage, perceived risk of unintended pregnancy, and perceived agency (or lack thereof). A contraceptive method mix that offers choice to its target users and that aligns method choices with distinct phases of the reproductive life cycle is vital to increasing contraceptive adoption and method continuation. For example: unmarried young women may want to prevent unintended pregnancies until they are married and thus may prefer long-term but reversible contraception methods; married women with no or few children may only want to be able to better space their pregnancies and thus may prefer on-demand or short-duration methods; and women whose families have reached their desired size may prefer longer-acting or permanent methods. Indeed, global efforts to expand access to modern contraceptives and to increase the range of contraceptive methods offered to women in developing countries – such as the Family Planning 2020 partnership and the United Nations 2030 Agenda for Sustainable Development – demonstrate the importance of choice in meeting women's needs and ultimately, in achieving development goals.

2.4 Role of Male Partners in HIV Prevention and Contraception Method Use

Another possible factor that may contribute to low (or high) adherence to a particular HIV/STI or pregnancy prevention method is male partners' attitudes about research studies, HIV prevention strategies, contraceptive methods, HIV treatment and prevention medications, intravaginal products, and/or oral tablets. In many countries around the world, especially in SSA, men are conferred the power to make health-related decisions for the family, including sexual and reproductive health issues. In some countries, 75% of women report that their male partners make health decisions related to women's health such as HIV-related prevention and treatment programs, including HIV testing and counseling, uptake and adherence to antiretroviral therapy (ART) and follow-up appointments.[74] Tackling traditional gender norms and gender inequality has been emphasized by UNAIDS as an important strategy to curb and reverse the HIV epidemic in that region.[75] Thus, men should be included in HIV prevention programs as their active participation is pivotal to the implementation and success of such programs.

When men actively participate in HIV prevention services like couples HIV testing and counseling, they and their partners experience multiple benefits. Studies suggest that people in couples who get tested together and mutually disclose their HIV status are more likely to adopt behaviors to

protect their partner than those who do not get tested or who get tested alone. In a serodiscordant couple, the provision of ART to the positive partner can significantly reduce the risk of transmission to the negative partner and the provision of oral PrEP to the negative partner can help to prevent HIV acquisition.[74]

Research shows that active involvement of male partners plays a positive role in increasing the effectiveness of female-oriented programs for reproductive health and HIV prevention and treatment, including women's uptake of HIV testing, uptake of and adherence to ART treatment, and selection of infant feeding options. In studies involving pregnant women, participants were more likely to accept HIV testing when their male partners attended antenatal visits with them during pregnancy[76] Women also reported a higher uptake of PrEP,[77] better adherence to ART treatment,[78,79] and better adherence to the recommended infant feeding option when their male partners participated in prevention of mother to child transmission (PMTCT) services.[77,80] Male partner engagement with PMTCT services was also positively associated with decreased infant HIV incidence and mortality and better HIV-free infant survival.[81-84]

A small number of studies explored possible adverse effects of male involvement in women's health and identified several potential drawbacks such as disruption of family relationships, physical violence and emotional abuse, and abandonment from partners and spouses.[85-88] In one study, participation in a PMTCT program in Malawi resulted in numerous divorces due to the program's request for partner disclosure.[89] In another study, women in a couples testing and counseling intervention group were significantly less likely to receive HIV testing and results than women in the control group with female individual counseling only.[90]

Despite those drawbacks, mounting evidence suggests that male involvement needs to be enhanced in HIV prevention and PMTCT programs. However, male partner participation levels are currently low in SSA. According to the WHO, the percentage of pregnant women in low- and middle-income countries receiving HIV testing increased from 21% in 2008 to 35% in 2010, with an increase from 45% to 61% in the highest burden areas of eastern and southern Africa, but the proportion of pregnant women who test with their partners is extremely low.[74] A survey of 388 men in Uganda also suggested that male participation in antenatal care was far from satisfactory, with only 5% of those surveyed ever accompanying their spouses to the antenatal clinic.[91] The lack of full male partner engagement represents one of the key obstacles to women's access to PMTCT services, and consequently may undermine the potential benefits of antenatal HIV prevention efforts.

Researchers have looked at factors affecting men's participation in their spouses' HIV antenatal care, and have identified barriers at multiple levels. Several review articles categorized these into societal/cultural, health system, information/knowledge, and individual-level barriers. The overriding societal/cultural barriers were the perceptions of antenatal care and pregnancy as purely a woman's affair. The gender norm that women are not allowed to lead men and the societal ridicule of men accompanying their wives to antenatal clinics were also important impeding factors.[92] At the health system level, long waits and a male-unfriendly atmosphere at the clinic, health workers' hostile attitude, and distrust in confidentiality of the health system were reported as major barriers.[93] At the individual level, some sociodemographic characteristics contributed to low male engagement, including older age, lower education, and lower income and/or resources.[83] Another set of barriers were related to men's information/knowledge gap, including the misconception that their HIV status is the same as that of their wives, limited knowledge of PMTCT, being unaware of the importance of male involvement, and availability of male-friendly HIV testing and counseling services.[85,92] Other frequently reported barriers included work commitments, financial burdens, and weakening of spousal relationships.[94-96]

Multiple facilitators to encourage male involvement in HIV prevention and PMTCT program were also identified and classified into similar groups at societal/cultural, health system and individual levels. Sending invitation letters to male partners to ask for their participation was identified as the first and foremost health system facilitator, followed by offering routine voluntary couples counseling, providing services in non-working hours and at sites other than antenatal clinics, encouraging open discussion among couples about HIV testing and counseling, organizing community sensitization activities, and providing antiretrovirals (ARVs) in health centers.[83,92] At the individual level, older age, higher level of education, previous experience of HIV testing, increased knowledge of HIV and perceived benefits of PMTCT were associated with better involvement in HIV-related antenatal care.[92,93] Other facilitators included monogamous marriage, stable relationship, open discussions of PMTCT among couples, and sero-concordant HIV status.[77,81,97]

In the context of research on HIV prevention and microbicides, a small subset of studies investigated the male partner's role in women's participation into microbicide clinical trials and product use. Even though microbicides have been designed as female-initiated products that help to promote women's autonomy and independence, studies demonstrated that male partners' understanding, awareness and acceptance of research trials and microbicides exert important direct and indirect influence on women's participation in studies as well as their self-reported product adherence.[98-100] In a clinical trial of a diaphragm and lubricant gel for HIV prevention, 995 Zimbabwean women were asked about their male partners' influence on their study participation and product use. Only 45% of female participants reported that their partner ''strongly'' supported the use of the diaphragm and gel, and only 31% and 26% of them said their partner ''strongly likes'' the diaphragm or gel, respectively. Another study synthesized findings of six qualitative studies on microbicide use in South Africa, Kenya, and Tanzania. It was found that most men either opposed their partners' participation in studies and their partners' use of microbicides, or provided only tacit permission to use microbicides, and only a minority provided active support, instrumental or emotional, to their partners for product use.[101] Secondary data (both qualitative and quantitative) from the ASPIRE, VOICE, CAPRISA 008, and other trials, as well as the above qualitative review, showed that for some women, microbicide use improved communication with partners, reinforcing product adherence.[102] However, it increased conflicts with partners and the risk of intimate partner violence (IPV) for others.

Microbicides were designed to give women an HIV prevention tool they can use without a male partner's involvement, but research suggests that the approval or support of male partners is often desired, or even required, to enable women to use microbicides. By investigating the role that male partners can have in women's preferences for DPP products, this study hopes to contribute to a greater understanding of how relationship dynamics can affect women's choices and decision-making related to their sexual and reproductive health.

2.5 Product End User Preferences

Placing end-users at the center of product development is now recognized as critical when designing products to meet the needs of target users.[103-106] End-user input is essential to the development of successful DPP products by informing product developers on how best to maximize a product's uptake and use, which ultimately maximizes its public health impact on the HIV epidemic.[107] In recent clinical trials of HIV prevention products, low product adherence was related to product acceptability and participants' sociocultural context, emphasizing the importance of integrating end-user perspectives early in the product development process.[108-110] End-user input will be critical to overcome those challenges by ensuring alignment between MPT

drug delivery forms still being developed, product attributes preferred by potential MPT users, and messaging to facilitate the adoption of MPT products.

Research engaging end-users as "co-designers" has demonstrated that understanding what product attributes are most influential to acceptability enables developers to make early product modifications and thus optimize a product's chances for success.[111-113] The TRIO and QUATRO studies combined the use of placebo products and DCE methodologies to understand young African women's preferences regarding a variety of MPT drug delivery forms in the context of HIV prevention.[112,114-116] These studies used preference weights and relative importance scores to identify from a range of product attributes (i.e., dosage, mode of delivery, pregnancy prevention) which features end-users found most important across product formulations. Injections were favored by a majority of TRIO participants (chosen by 64% of participants after 3 months of using each of three products), but otherwise there were no clear favorites among the hypothetical MPT products evaluated in TRIO (oral tablets, VR, injections) or in QUATRO (VR, vaginal film, vaginal insert, vaginal gel). Product familiarity seemed to be a key component of participants' preferences in both studies, given the increases in product ratings over time and with product use experience, as well as the preference for injections in TRIO, a widely prescribed method of contraception delivery in SSA. Lastly, although efficacy was rated as the most important product attribute in QUATRO, participants were willing to accept less efficacious methods if they exhibited other positive attributes (e.g., discreetness, ease of use, prevents pregnancy). Studies like TRIO and QUATRO underscore the importance of providing a menu of prevention choices to fit the variety of settings in which women live.

In the context of HIV prevention, most end-user research conducted to date has focused on the individual. However, many women engage their male partners in some capacity when making decisions about HIV prevention, and often these decisions are made jointly.[101,117] Likewise, as described in Section 2.4, relationship contexts (e.g., commitment level, trust, duration) influence women's adoption of HIV and pregnancy prevention. Therefore, it is just as important to develop couples-based intervention approaches as it is to develop products that can be used discreetly by women without their male partner's knowledge. To do so, it is criticial to identify what MPT product attributes are valued most by couples across geographic settings and contexts, and to understand how members of a couple make decisions regarding HIV and/or pregnancy prevention.

2.6 Rationale for Study Design

MTN-045 is designed to identify factors that may affect acceptability of and adherence to DPP product use. MTN-045 will elicit couples' preferences about various drug delivery forms currently in the MPT product development pipeline. MTN-045 will also explore the reasons for those preferences, including the role of the contextual environment, with a specific focus on partner influences. The socio-cultural context,[118] including the organization of women's social environment (e.g., living arrangements, relationship factors, family members, and the larger social network) and individual beliefs and attitudes about HIV risk and/or contraception, may influence these preferences. Although some studies show that male partners play an important role in women's adherence to HIV prevention[119] and in contraceptive decisions, the focus on couples as end-users of future DPP products addresses gaps in understanding male partners' interest in DPP products and their influences on women's preferences for those products.

Besides an overall preference for long-acting injectables likely due to widespread familiarity with injectable contraceptives[116,120], there is little known about what other types of drug delivery forms women in SSA would like to see made available. MTN-045 will use behavioral questionnaires,

including Discrete-Choice Experiments (DCE) and joint decision tasks, and qualitative in-depth interviews (IDI) to explore DPP product preferences for this population. An in-depth understanding of the various socio-behavioral factors that contribute to DPP product preferences, including male partner attitudes, may inform implementation of future strategies to overcome acceptability and/or adherence challenges, starting with the design of the products themselves.

3 OBJECTIVES

3.1 Primary Objectives

- To determine heterosexual couples' preferences for a DPP product to inform product delivery and future product design to maximize uptake and willingness to use among sub-Saharan African heterosexual couples.

- To assess the level of influence of the male partner on a woman's preferences for a DPP product and on her decision-making process regarding product preferences and use.

3.2 Secondary Objectives

- To identify factors that may influence DPP product interest and preferences in heterosexual men, women and couples, including individual and relationship characteristics, and product "positioning" (i.e., contraceptive+HIV prevention vs. HIV prevention+contraceptive).

- To examine differences in preferences and individual vs. joint decision-making by several sociodemographic factors, including age of the woman (e.g., 18-24 vs. 25-40) and parity (nulliparous vs. parous).

3.3 Exploratory Objectives

- To explore relationship dynamics and their influences on the decision-making process for individuals and couples.

- To explore the extent to which male partner interest for, or acceptance of, a DPP product influences the female partner's willingness to use the product.

- To estimate uptake of a range of potential DPP products that can be incorporated in cost-effectiveness modelling of future products.

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-045 is a cross-sectional study that will utilize questionnaires, including DCEs and joint decision tasks, to assess heterosexual couples' preferences related to DPP products that could

be used to prevent unintended pregnancies and HIV infection. A subset of couples will complete an IDI designed to explore DPP product-related decisions.

4.2 Description of Study Population

The MTN-045 study population will consist of heterosexual couples of reproductive age who meet eligibility criteria as described in Sections 5.3 and 5.4.

4.3 Time to Complete Accrual

Approximately 12-15 months for recruitment and enrolment at each site.

4.4 Expected Duration of Participation

Most participants will complete all study procedures in a single study visit, including administrative and data collection procedures. Participants who are selected for an IDI may require a second study visit if it is not feasible to complete the IDI at the initial visit. Additional visits may be conducted to complete all required procedures, if necessary.

4.5 Sites

MTN-045 will be conducted at clinical research sites (CRS) in SSA selected by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population

A sample of approximately 400 heterosexual couples will be selected for participation in this study. Inclusion and Exclusion Criteria, Sections 5.3 and 5.4, respectively, are used to ensure the appropriate selection of study participants for MTN-045.

5.2 Recruitment

Participants will be recruited from the communities served by the selected CRS. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives will advise on these materials before they are submitted to the IRB/EC for review. Community education strategies, including group sessions, may be employed as part of participant outreach. Site staff may work with community stakeholders, including community advisory board (CAB) members and voluntary health workers, to identify and recruit a community-based sample of couples. Potential participants may be asked about their interest in contraception and/or HIV prevention during pre-screening activities to ascertain presumptive eligibility to enroll in MTN-045; see Section 13.5 for additional details.

5.3 Inclusion Criteria

Each member of the couple must meet all of the following criteria to be eligible for inclusion in the study, and both members of the couple must be willing and eligible for the couple to enroll:

1. Able and willing to provide written informed consent in one of the study languages.

2. Able and willing to complete the required study procedures.

3. Currently in a heterosexual relationship (living together or not) for at least 3 months (by self-report) with the other member of the couple.

4. At time of Enrollment, expressed interest in contraception and/or HIV prevention (by self-report).

For female partner:

5. Between the ages of 18 to 40 years (inclusive) at Enrollment, verified per site standard operating procedures (SOPs).

6. HIV negative (by self-report).

For male partner:

7. Aged 18 years or older at Enrollment, verified per site SOPs.

5.4 Exclusion Criteria

Potential participants who meet the following criteria will be excluded from the study along with their partner:

1. Has any significant medical condition or other condition that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed consent, make study participation unsafe (including risk for IPV as a result of study participation), complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

6 STUDY PRODUCT

MTN-045 will not involve the administration of any study product.

7 STUDY PROCEDURES

7.1 Study Visits

Approximately 400 couples will be enrolled (see Section 10.3 for sample composition details). Participants may be screened either separately or together with their partner, and site staff may explain the study to participants either separately or together with their partner, but other key components of participants' consent will be solicited separately to reduce the potential for participant coercion (see Section 13.5 for additional details).

Survey questionnaires will be administered to each member of the couple separately. The individual questionnaires will be followed by a joint couple decision task completed by the couple together. Prior to completing the questionnaires, enrolled participants will receive an introduction to DPP products using standardized materials.

A subset of up to 80 participants (i.e., one or both partners from up to 40 couples) will be selected to complete a single post-survey explanatory IDI to provide further insight on the participants' survey responses and on any unexpected and/or interesting examples of experiences and behaviors relevant to the study endpoints.

Study visits may take place at the study clinic, at the participant's home, or at any other location agreed upon by the participant(s) and the study staff. Multiple visits may be conducted to complete all required procedures, if necessary.

7.1.1 Screening and Enrollment Visit Procedures

Table 1: Screening and Enrollment Visit Procedures

Screening and Enrollment Visit	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Obtain written informed consent for screening and enrollment • Assign a unique Participant Identification (PTID) Number • Collect demographic data • Collect locator information • Provide reimbursement for study visit • Schedule next visit (if applicable)
Behavioral	• Provide introduction to DPP products via standardized materials • Administer behavioral questionnaire(s) individually • Administer behavioral questionnaire(s) as a couple

7.1.2 In-depth Interview Visit Procedures (for subset of participants only)

Table 2: In-depth Interview Visit Procedures

In-depth Interview Visit	
Component	**Procedures**
Administrative and Regulatory	• Update locator information • Provide reimbursement for study visit
Behavioral	• Conduct IDI

The IDI Visit may occur on the same day as the Screening and Enrollment Visit if agreed upon by the participant(s) and the study staff, but may be scheduled up to 28 days after the Screening and Enrollment Visit.

7.2 Behavioral Evaluations

The study will address questions related to the primary and secondary objectives of determining heterosexual couples' DPP product preferences and the underlying factors influencing those preferences, from the perspective of both partners in the couple. These questions will be assessed via behavioral questionnaires and IDIs conducted by trained interviewers. In addition, the study aims to gain further insight on:

- Motivations for DPP product use among couples with varying levels of risk for unintended pregnancy or HIV infection
- Motivations for DPP product use among couples with varying levels of male partner influence on the female partner's decision-making
- What effect, if any, knowledge of the product's efficacy would have on product preferences
- DPP product uptake, positioning, and other product roll-out issues

Additional questions and probes will be designed to delve further into the social and cultural norms that may play a role more broadly in DPP product preferences.

7.2.1 Survey Questionnaires

Participants will complete survey questionnaires, first separately from their partner, followed by a joint couple decision task where the couple will be asked to jointly indicate product attribute preferences and dislikes. The following will be assessed for all participants:

- Individual and relationship characteristics
- Interest in and willingness to use a DPP product
- Preferences among attributes of a DPP product

The survey questionnaires will measure preferences for a hypothetical DPP product by asking participants to select the products they would choose to prevent HIV and pregnancy from pairs of products with varying sets of attributes. Following each choice question, participants will be asked their preference between their chosen product and male condoms. They may also be asked to compare their preferred product, among those assessed, to longer-acting delivery forms such as injections or implants. Attributes may include:

- Product form (e.g. vaginal ring, oral tablets, vaginal insert, vaginal film)
- Duration or frequency of use
- Side effects
- Whether STI prevention could be included in product indication
- Whether it can be detected during sexual intercourse
- Hormonal vs. non-hormonal contraceptive

7.2.2 In-Depth Interviews (IDIs)

A subset of couples will be asked to complete an IDI. Site staff may ask one or both partners to complete an IDI, and IDIs may be conducted either individually or as a couple. IDIs will include, but not be limited to, topics such as:

- Communication and decision-making within the relationship, both for sexual and reproductive health decisions and for more general decisions
- Descriptions of HIV and pregnancy prevention practices
- Main challenge(s) and facilitator(s) encountered with use of contraceptive methods
- Main challenge(s) and facilitator(s) encountered with use of HIV prevention methods
- Other factors (e.g., situational, relationship, social/cultural/economic, sex and menstruation related, etc.) influencing potential DPP product use patterns (e.g., uptake, sustained use)
- Recommendations for "real world" implementation (e.g., overcoming financial barriers, marketing of DPP products)

IDI guides will be developed by qualified social scientists and administered by qualified interviewers. Guides will contain key research questions relating to the main topics of interest and suggested probes. Interviews and discussion sessions will be audio-recorded and transcribed into English (using a 1-step translation/transcription process).

Various tools may be used to facilitate interviews and discussion of sensitive topics with IDI participants. These may include, but not be limited to, visual displays of various drug delivery forms and show-cards listing topics and themes previously elicited in other studies.

8 ASSESSMENT OF SAFETY

MTN-045 is a minimum-risk research study. It does not involve a study product nor involve clinical, laboratory or other procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation; see Section 13.4.1 for expected risks of study participation. The study site IoR is responsible for continuous monitoring of all study participants and for alerting the protocol team if unexpected safety events arise. Study sites will have written procedures for ensuring prompt reporting to the IRB/EC of any unanticipated problem involving risks to subjects or others. No safety events will be captured in the study database, except for social harms (see Section 8.2).

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants, and for alerting the protocol team if unexpected concerns arise. Since the safety risks are minimal in this study, if any such unexpected concerns arise, site study staff must make the site IoR aware. The site IoR will provide follow-up guidance to the appropriate on-site staff member (e.g., site clinician, counselor, nurse, etc.). Study sites will take steps during pre-screening and screening activities to minimize the potential for partner coercion or for placing participants at increased risk of IPV; see Section 13.5 for details. Additionally, an SOP for emergency procedures will be developed for the MTN-045 site staff to be used in situations of social harm and when situations that require immediate attention are identified, including IPV and suicidal ideation or behavior. The SOP will provide clear guidelines for site staff to refer participants in these situations to the relevant institution/body and to provide feedback to the protocol team.

The Manual for Expedited Reporting of Adverse Events to DAIDS will not be used for this study for the following reasons: 1) this study does not involve a study drug and is non-invasive; and, 2) adverse events are not primary or secondary objectives of the study. Untoward clinical or medical

occurrences reported by study participants to have been experienced during study participation will be recorded in participant file notes.

8.2 Social Harms

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 social harms – non-medical adverse consequences – may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be related to study participation will be captured via case report form (CRF) and reported to the DAIDS Medical Officer (MO), Protocol Chairs, and responsible site IRBs/ECs according to their individual requirements beginning at the time of enrollment (i.e., after participants sign the informed consent and eligibility is confirmed) until study participation is complete. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-045 Study Specific Procedures (SSP) Manual. While maintaining participant confidentiality, study sites may engage their CABs in exploring the social context surrounding instances of social harm.

9 CLINICAL MANAGEMENT

There are no additional clinical management considerations for participants enrolled in this study. Participants who express concerns with social, psychological or clinical issues will receive appropriate care and counseling to the extent possible, and/or be referred for appropriate care to services available at the CRS, or at nearby partnering facilities.

9.1 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR 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 for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may do so if the accrual target has not yet been met.

10 ANALYTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

MTN-045 is a cross-sectional study that will utilize questionnaires, including DCEs and joint decision tasks, and IDIs to assess heterosexual couples' preferences related to DPP products that could be used to prevent unintended pregnancies and HIV infection.

One main goal of the study is to determine heterosexual couples' preferences for a DPP product to inform product delivery and future product design to maximize uptake and willingness to use among sub-Saharan African heterosexual couples. Another main goal of the study is to assess the level of influence of the male partner on a woman's preferences for a DPP product and on her decision-making process regarding product preferences and use.

Secondary objectives of the study include:

- To identify factors that may influence DPP product interest and preferences in heterosexual men, women and couples, including individual and relationship characteristics, and product "positioning" (i.e., contraceptive+HIV prevention vs. HIV prevention+contraceptive).
- To examine differences in preferences and individual vs. joint decision-making by several sociodemographic factors, including age of the woman (e.g., 18-24 vs. 25-40) and parity (nulliparous vs. parous).

10.2 Study Endpoints

The study will examine DPP product preferences of heterosexual couples in SSA. Survey questionnaires will be conducted with each enrolled participant, first separately from their partner and then in conjunction with their partner. In particular, the survey questionnaires will focus on the following primary and secondary endpoints:

- Attributes of a DPP product that influence preferences among heterosexual couples.
- Differences in DPP product attribute preferences when comparing individual to couples' choices (e.g., woman's individual preferences vs. preferences indicated through the joint couples decision task).
- Salient relationship-based and decision-making factors that influence DPP product interest and preferences.
- Differences in attributes salient to preferences by sociodemographic factors such as age and parity that may reflect lifecourse stage.

A single IDI will also be conducted with a subset of up to 80 participants (i.e., one or both partners from up to 40 couples) enrolled in the study in order to gain additional insight on their responses to the survey questionnaire topics above. This IDI will explore participants' interest in and preferences for a DPP product, relevant challenges and facilitators of prior contraceptive and/or HIV prevention product use, social and relationship dynamics that influence decision-making, and any recommendations for future product implementation.

10.3 Sample Size and Composition

The study will enroll approximately 400 heterosexual couples across the study sites. Women who are currently using contraceptives as well as those not using contraceptives will be eligible. Couples who are living together as well as those not living together will be eligible. Community-based recruitment will be conducted through stakeholder engagement with consulation from CAB members. Participants will complete survey questionnaires, first separately from their partner, then followed by a joint couples' decision task. Up to 80 participants, i.e., one or both partners from a subset of up to 40 couples, will be selected to complete an IDI.

10.4 Data and Study Monitoring Procedures

Demographic and behavioral data will be captured electronically on tablet computers. Qualitative data will be audio-recorded, translated and transcribed in English, and coded for thematic analyses using Dedoose or a similar qualitative software. RTI International will function as the overall data coordinating center for quantitative and qualitative data and will lead all analyses.

No Study Monitoring Committee (SMC) review will be performed for MTN-045 given the non-clinical nature of the study. Protocol team members from the MTN, including RTI International and FHI 360, will provide oversight of study operations and ensure the study is implemented in accordance with MTN standards, as defined in the MTN Manual of Operating Procedures.

10.5 Data Analysis

10.5.1 Quantitative analysis – Primary endpoints

A random parameters logit (RPL) model will be used to estimate preferences for the attributes of a DPP product. The model will include a parameter for the couple to account for the clustered structure of the data. The preference weight estimates from the RPL model will be used to estimate which attribute of a DPP was most influential on participants' product choice.

The level of discordance between the woman's individual preference and the couple's preference will be described by counts and frequencies. A regression model will be used to estimate congruency between the woman's individual preference and the couple's joint preferences, by using the woman's preference to predict the joint preference.

10.5.2 Quantitative analysis – Secondary endpoints

To explore differences in preferences by relationship-based indicators and sociodemographic factors (such as age and parity), separate random parameter logit models will be estimated with interaction terms between the factors of interest and attribute levels. Additional methods, such as latent class analysis, may be used to explore preference heterogeneity by identifying sub-groups defined by distinct sociodemographic, behavioral and relationship-based characteristics with varying preferences. The study analysis plan will explain the application of these analytic approaches in greater detail.

10.5.3 Qualitative analysis

Data Sources

The qualitative data from MTN-045 will include three main data sources:

- Original handwritten interview notes and observation checklists (questionnaires and IDIs)
- Audio-recorded IDIs
- Transcripts of IDIs

Qualitative data will be audio-recorded, translated and transcribed in English, and coded for thematic analyses using Dedoose or a similar qualitative software.

Qualitative Analysis Overview

The following section provides a brief overview of the analysis process; however, a more detailed description of the qualitative analysis will be presented in the study analysis plan.

Qualitative analyses from the MTN-045 study will use a variety of techniques to provide an in-depth characterization of the contextual factors that affected participants' DPP product preferences. The primary source of qualitative data used in the MTN-045 analysis will consist of raw textual data. Qualitative data will be audio-recorded, translated and transcribed in English, and coded for thematic analyses using Dedoose or a similar qualitative software. Data coding will be used as a primary analytical approach for data reduction; that is, to summarize, extract meaning, and condense the data.[121,122] MTN-045 transcripts will be coded first through descriptive coding for key themes and topics, using a preliminary codebook (see Section 10.5.4).[123] Additional codes will be identified through an iterative process of reading the textual data to identify emergent themes, and the codebook will be modified accordingly. In addition to descriptive codes, pattern codes, which achieve a greater level of abstraction, will be used to start linking themes and topics together in order to explore the relationship between socio-contextual factors and product preferences, as well as between product attributes and preferences.[121] Whenever possible, we will also compare study sites and explore differences or similarities related to product preferences due to different socioeconomic, cultural and geographical contexts. The analysis will be done by the investigative team, working interactively through emails, and regular phone or face-to-face meetings. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data.[124] Whenever possible, site staff will be involved to corroborate findings from the analysis team.

10.5.4 Codebook Development and Coding Process[125]

Coding is an essential process for data reduction necessary for the management and interpretation of large amounts of qualitative data. Staff at RTI International will develop a codebook and study procedures for coding and analysis of all of the qualitative data. Each code will be operationally-defined and refined in an iterative way, as needed. Transcripts will be coded using a qualitative software package such as Dedoose.

During the study development stage, a set of preliminary codes will be developed based on the research questions of this study. The analysis coding structure will be hierarchical, and will reflect the topics/themes covered in the interview guides. After the first 2-3 interviews are completed, each member (analyst) of the coding group will apply this initial set of thematic codes to a common transcript, discuss their coding experiences (via email, a meeting, or conference call), and agree on expanding and modifying code names and definitions when necessary. The coding team will generate substantive and conceptual categories through an iterative process of reading the data, and generating codes based on the data and on key themes or topics identified *a priori*, applying the codes to the data, and refining these as coding progresses. Thus, codes will be centered on the main topics of interest (e.g., product preferences: product attributes influencing product initiation, persistence and implementation, and environmental challenges and facilitators of product use) and the hypothesized contextual spheres of influence. However, by nature, the qualitative research process is iterative, and the Dedoose software allows for the generation of new codes for emergent themes that were not identified *a priori* by the research team. The software also allows for coders to insert descriptive comments and memos to themselves and others as they are working, and to code for concepts not spelled out in verbatim text, such as "contradiction," when a participant contradicts herself.

Once finalized, the codebook will be used for coding of all of the transcripts. Comprehensive listings of all coded quotations for every code (as well as “families” of related codes) will be generated in Dedoose. The coding team will consider the coded dataset in its entirety, and “stratify” the coded quotations by factors such as the site, relationship dynamics, reported opinions of preferred product attributes, or reported opinions of environmental challenges and facilitators of product use. These stratifications will depend on findings from the analysis of these data clusters.

The coding process will involve a core group of at least 2-3 analysts who will frequently communicate (via email, phone or in person meetings) and discuss their use of the codebook and application of the codes during the coding process. Inter-rater reliability will be assessed among all coders on a pre-selected proportion of transcripts via use of Dedoose or other coding software tests. Following this process, the coding team will discuss (in person or via teleconference) the coding discrepancies, which will ultimately be resolved through consensus. Regular discussions among the coding team will ensure that coding remains standardized and reliable.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study data will be collected electronically on password-protected tablet computers. Interview data will be digitally transferred to a secure electronic database. Data will be routinely backed up to a server housed by RTI International, where all electronic data will be stored on secure, password-protected computers accessible by key study personnel only. Quality control (QC) reports and queries routinely will be generated and distributed by RTI International to the study sites for verification and resolution. As part of the study activation process, each study site must identify all electronic interview files to be used as source documents.

IDI guides will be developed by RTI International in conjunction with the protocol team and, where required, will receive IRB/EC approval. Source documents include audio files, transcripts, observation checklists and interview notes. Transcripts of IDIs will be generated using the audio recordings. The transcripts will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and analyzed using a qualitative software package. Interview audio files, observation checklists and notes will be kept at the site in the participant files. RTI International will act as a hub, and manage all data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. Transcripts will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf).

For MTN-045, source documentation may include recruitment logs, enrollment records, visit checklists, paper CRFs, electronic interview data, participant file notes, and electronic audio files. Essential documentation for the study also includes all versions of the protocol, informed consent forms, operating procedures and key communication with the protocol team. In accordance with U.S regulations, each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study.

Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by DAIDS. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS.

11.3 Quality Control and Quality Assurance

At the field level, designated staff will verify electronic data collected are reflected in weekly reports and check the quality of the translated IDI transcripts to ensure that they reflect the content of the interview. Electronic interview data and IDI transcripts will be reviewed at the site and transmitted to RTI International where they will be reviewed and queried. All queries will be resolved through a standardized QC reporting mechanism.

All study sites will conduct QC and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported CRS (https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf).

12 CLINICAL SITE MONITORING

RTI International staff or designees will review study records during the course of the study. However, no formal clinical monitoring will be conducted. RTI Internatinal staff or designees will do the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Assess implementation and documentation of internal site quality management procedures

The IoR/designee will allow inspection of study facilities and documentation (e.g., informed consent forms, clinic records, other source documents, CRFs), as well as observation of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the US OHRP, NIH, NIAID, and/or contractors of the NIH, and other local, US or international regulatory authorities, including site IRBs/ECs, and representatives of the MTN, as needed. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Boards/Ethics Committees

Site investigators will make every effort to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB/EC approval. The IoR/designee will permit audits by the NIH, local authorities, site IRBs/ECs, the MTN, OHRP, other local, US, or international regulatory authorities, or any of their appointed agents.

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent form, and study-related documents as required, are reviewed by an IRB/EC responsible for oversight of research conducted at the study site. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Each IoR/designee will make progress reports to the IRBs/ECs within three months after study termination or completion, unless specified otherwise by their IRBs/ECs. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. More real-time or frequent reporting of one or more of these or other items may need to be furnished if so specified by their IRBs/ECs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the most current DAIDS policies at the time of registration.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the 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 sites 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. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet 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. Site-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 should 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.

13.3 Study Coordination

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair(s) and DAIDS MO. Study implementation will be guided by a common SSP manual that provides further instructions and operational guidance on conducting study procedures and associated data processing. Standardized study-specific training will be provided to all sites by RTI International and other designated members of the protocol team.

13.4 Risk Benefit Statement

13.4.1 Risks

It is not expected that this study will expose human subjects to unreasonable risk. Participation in this research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors and DPP product preferences.

Psychological Harms

MTN-045 will ask questions that may cause individuals discomfort given their personal nature. Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics, particularly during the couples' interview. This could result in undesired changes in thought and emotion or in tension within the couple.

While steps have been taken to minimize the risk of psychological harms (see Section 13.5 for details) and while study staff will inform participants that they can choose not to answer questions at any time, study staff will collect information on participants who report a change in mood as a result of study participation. In addition, study staff will ensure that participants have access to proper clinical resources to address psychological harms.

Social Harms

Although study sites 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 social harms may result (i.e., because participants could become known as HIV-positive or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Furthermore, it is possible that talking about one's own behavior or attitudes on sensitive topics during the couples' interview could lead to relationship problems for one or both partners. It is also possible that one partner could be coerced into study participation by the other, or that study

participation could put one partner at increased risk for IPV. Sites will take steps to minimize those possibilities (see Section 13.5 for details).

Data on the occurrence of social harms will be collected from all participants. These data will be captured via CRF and analyzed on an ongoing basis. The protocol team will monitor, evaluate and adjust operations to reduce the potential for such occurrences.

13.4.2 Benefits

There are no direct benefits to participating in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader development and implementation of DPP products. Participants may also appreciate the opportunity to contribute to the fields of HIV prevention and contraception research.

Lastly, the information that participants provide may help health professionals develop better ways to improve communication and understanding between researchers and participants in HIV prevention and contraception studies.

13.5 Informed Consent Process

Each study participant will provide written informed consent prior to completing any study procedures. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf) and the relevant source documentation appendix (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

In addition to informed consent forms, the protocol team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, which will be detailed in the MTN-045 SSP Manual. For example, potential participants may be asked to disclose their interest in HIV prevention and contraception during pre-screening activities to ascertain presumptive eligibility to enroll in MTN-045. Potential participants may also be privately asked whether they believe that participation in MTN-045 could place them at risk for experiencing IPV. Study staff will explain to all participants that some of the study activities, including some of the questionnaires, will be completed together with their partner. Only those potential participants who express interest in HIV prevention and/or contraception, and only those potential participants who do not express IPV-related concerns and/or do not raise concerns about participant safety among study staff, would be considered for further screening.

Study staff will explain the study to both members of the couple and determine their presumptive eligibility to participate in the study; both of these informed consent process components may be done with the potential participants either separately or together as a couple. However, to reduce the potential for coercion, study staff will assess each participant's willingness to be in the study and confirm their eligibility separately from their partner; participants will also sign individual

consent forms and have an opportunity to ask questions about the study separately from their partner.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process will specifically address the following topics of importance to this study:

- The purpose of the study.
- The potential social harms associated with study participation (and what to do if such harms are experienced).
- There is no benefit to taking part in this study.
- The right to withdraw from the study at any time.

13.6 Participant Confidentiality

All study procedures will be conducted in a location agreed upon by the participants, and every effort will be made to protect participant privacy and confidentiality. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All study data collection and administrative forms will be identified solely by PTID number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms, will be stored securely. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PTID numbers to identifying information will be stored in a locked file in an area with limited access. All digital audio files will be stored on password-protected computers. Audio files will be transcribed in English (using a 1-step translation/transcription process) and securely stored. Please see MTN-045 SSP Manual for guidance. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US OHRP, NIH, and/or contractors of the NIH, and other local, US, or international regulatory authorities
- Study staff
- Site IRBs/ ECs
- RTI International
- FHI 360
- Study monitors

13.7 Special Populations

13.7.1 Pregnant Women

Pregnancy is not exclusionary. Due to the nonclinical nature of this study, no pregnancy-related risks are anticipated in MTN-045.

13.7.2 Children

MTN-045 will enroll participants who are aged 18 or older at the time of Enrollment, as verified per site SOPs, thus children will not be considered eligible for this study.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms.

13.9 Study Discontinuation

This study may be discontinued at any time by NIH, the MTN, the US OHRP, other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies will govern publication of the results of this study.

15 APPENDICES

APPENDIX I: SCREENING AND ENROLLMENT SAMPLE INFORMED CONSENT FORM

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-045

Dual Purpose Prevention (DPP) Product Preferences among Couples

Version 1.0

February 25, 2019

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Couple User Preferences in Dual purpose prevention products (CUPID)

INFORMED CONSENT

IMPORTANT INFORMATION ABOUT THE RESEARCH STUDY

You and your partner are being asked to take part in this research study because you are a man and a woman who have been sexual partners for at least three months and are interested in contraception, HIV prevention, or both. Approximately 400 couples like you will participate in this study at two research sites in Uganda and Zimbabwe. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Important things you should know:

- There are no study products (investigational drugs or other products) for you to use in this research study.
- The purposes of the study are to understand:
    - What couples value when choosing a dual purpose prevention (DPP) or "2-in-1" product meant to prevent unintended pregnancies and HIV infection,
    - What affects couples' preferences for these products, and
    - How couples make decisions together and as individuals when thinking about using these types of products.
- If you and your partner both qualify and choose to participate, you will be enrolled in the study and asked to answer questions alone and also as a couple. For most couples, the total length of your participation in the study will be one visit of approximately [X] hours.
- You and/or your partner may also be selected to complete a more in-depth interview, where you will be asked to talk about your responses. If you are selected for this additional interview, you may complete it at the same visit or be asked to have a second study visit of approximately [X] hours on a different day.

- Some risks or discomforts from participating in this study include:
    - Feeling uncomfortable with some of the questions study staff may ask about your sexual behaviors and relationships, and
    - Risk of conflict in your relationship if you or your partner are upset by discussions of sex, contraceptive choice, or HIV prevention.
- You will not experience any direct benefit from participation in this study, but you may learn more about HIV and ways to protect yourself from acquiring HIV. You may also learn about contraception and ways to plan pregnancy.
- Taking part in this research project is voluntary. You do not have to participate and you can stop at any time. This will not affect the service you get at the research clinic or clinics in surrounding areas.
- If you or your partner decide not to join this study, there may be other studies you can join if you meet their requirements. Study staff can provide you with additional information about those studies if you are interested.

Before you and your partner decide if you want to continue in this study, we want you to learn more about the MTN-045 study. This consent form gives you information about this study. Study staff will talk with you and answer any questions you may have. Once both of you read and understand this study and its requirements, you can decide if you want to take part in it. If you decide to take part in MTN-045, you will sign your name or make your mark on this form. A copy of this document will be offered to you. Your partner will sign a separate copy of the same form.

Your and your partner's eligibility to participate in this study will then be assessed, and once confirmed, you and your partner will be considered enrolled in the MTN-045 study.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer at the end of this form for more information).

WHAT IS THE PURPOSE OF THIS STUDY?

You and your partner are being asked today to take part in MTN-045. The main goal of this study is to better understand couples' preferences related to dual purpose prevention (DPP) products. DPP products are "2-in-1" products that could be developed to help prevent both HIV and unintended pregnancies. These include products such as vaginal rings, vaginal inserts, vaginal films, and oral tablets. You will be given more information about these products prior to completing the interviews.

You will be asked questions individually and with your partner. Some couples will be asked to participate in an in-depth interview (IDI). Study staff will tell you if you are going to be asked to take part in an IDI.

STUDY PROCEDURES

The MTN-045 study consists of one study visit, which will take place today after you and your partner sign/mark copies of this informed consent form. If you and/or your partner are asked to participate in an IDI, the IDI may take place today if you prefer and if scheduling allows. If not, it may take place on a different day that is convenient for you

and/or your partner. Additional visit(s) may be conducted to complete all required procedures, if necessary. Visits will take place at a place agreed upon by you, your partner, and the study staff, which may be the study clinic, your home or another convenient location ***[SITE TO INCLUDE ALTERNATE LOCATION]*.**

The procedures done at this visit will take about ***[SITE TO INSERT TIME]***.

- Study staff will ask you where you live and other questions about you, and your understanding of the study requirements.
- You and your partner will complete some questionnaires individually, and will also complete some questionnaires together as a couple:
    - Study staff will ask you questions and record the answers using a computer.
    - The questionnaire will be completed in a private location.
    - You will be asked to decide which DPP product you would prefer to use based on their different characteristics.
    - After the interviewer has read through the first few questions and response choices, you will be allowed to read and respond to the remaining questions on your own, if you prefer.
    - Study staff will not share the information you provide during the invididual interview with your partner.
    - Couples will be asked to make choices about DPP products together. The interviewer may ask you to explain why you made your choices, and may take notes.
    - The interviewer will also ask questions about:
        - Your age, education level, health, relationship status, and employment status.
        - Your views about HIV risk and prevention, pregnancy risk and contraception, sexual history, existing prevention methods, and aspects of your relationship.
        - We ask these questions to get a full understanding of your needs as a potential user of a new DPP product.
- You and/or your partner may be asked to have an IDI:
    - You will have an IDI in the presence of one or two MTN-045 research staff members. The IDI will take approximately ***[SITE TO INSERT TIME]***. Study staff will make every effort to ensure your privacy and confidentiality. Information you provide during the IDI will not be shared with your partner without your permission.
    - During the IDI, the interviewer will talk with you about your answers to the study questionnaires and may take notes. Interviews will be audio-recorded to make sure we record your words exactly how you said them.
    - The interviewer will also ask you questions about:
        - Your experience with and motivations for using contraceptive and/or HIV prevention methods.
        - Possible ways to promote DPP product use.
- Study staff will also:
    - Inform you about other available health and social services, if needed.
    - Schedule your next visit, if necessary.

- Reimburse you for your visit(s).

RISKS AND/OR DISCOMFORTS

During the interviews (questionnaires and IDI), you and your partner may be asked some questions that cause you to feel embarrassed or uncomfortable, especially when your partner is present during the interview. You may become embarrassed and/or worried when discussing sexual practices or your opinions about contraceptive or HIV prevention strategies. Trained study interviewers will help you deal with any feelings or questions you have. You can choose not to answer questions at any time.

Another possible risk of this study is loss of confidentiality of the information you and your partner give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, interviews (questionnaires and IDI) will take place in private, and study staff will not share your responses during the individual interviews with your partner. The information recorded during your interviews will be strictly protected, kept confidential, and only use study numbers or fake names. This means that no one other than the MTN-045 interview team will be able to link your responses to you personally. Your interview responses and any other information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-045 study team for the purposes of this research. *[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/ECs:* Your interview responses, including the audio recordings and notes from these materials, will be kept for a minimum of at least three years after completion of this research.]

It is possible that others may learn of your participation here and, because of this, may treat you and your partner unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. It is also possible you may experience problems in your relationship because of your participation in this study. For example, you may experience an increased risk of relationship conflict, including violence or physical injuries, if you or your partner are upset by discussions of sex, contraceptive choice, or HIV prevention. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them. We may also refer you to other organizations for support if needed.

BENEFITS

There are no direct benefits to you or your partner from participating in this study. However, you and others may benefit in the future from information learned in this study. Participants in this study may also appreciate the opportunity to contribute to HIV prevention and contraception research efforts. Information participants provide may help researchers improve DPP products in development as well as counseling materials about DPP product use. Lastly, the information provided in this study may help health professionals develop ways to improve communication and understanding between researchers and participants in HIV prevention and contraception studies.

Medical care for HIV infection and other health conditions will not be part of this study. This study cannot provide you or your partner with general medical care, but study staff

will refer you to other available sources of care, if needed.

NEW INFORMATION
You will be told of any new information learned during this study that might affect your willingness to stay in the study. You will also be told when study results may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT
You may be removed from the study early without your permission if:

- The study is cancelled by the US NIH, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB) or Ethics Committee (EC). An IRB or EC is a committee that watches over the safety and rights of research participants
- Either you or your partner is unwilling or unable to comply with required study procedures, including study visit attendance.
- Deemed necessary to protect your or your partner's safety.
- Other reasons that may prevent either you or your partner from completing the study successfully.

COSTS TO YOU
There is no cost to you or your partner for study-related visits.

REIMBURSEMENT
[*SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT*]: You will receive ***[SITE TO INSERT AMOUNT $XX]*** for your time, effort, and travel to and from the visit location at each scheduled visit.

CONFIDENTIALITY
Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff may use your personal information to verify that neither you nor your partner are in any other research studies. This includes studies conducted by other researchers that study staff may know about.

Any publication of this study will not use your name or identify you personally. The information collected during your interviews could be used for future research by our research team or other researchers without notifying you or asking your permission for this use. However, only study numbers or fake names will be linked to your responses, and no one other than the MTN-045 interview team will be able to link your responses to you personally.

Your records may be reviewed by:

- The Research Triangle Institute International
- Site IRBs/ECs
- FHI 360

- Representatives of the US Federal Government, including the US OHRP, NIH and/or contractors of NIH, and other local, US, or international regulatory authorities
- Study monitors
- Study staff

[Sites to remove/amend the following if instructed by their local IRB/EC:]
The researchers will do everything they can to protect your privacy and that of your partner. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This Certificate protects study investigators from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you or your partner give for study purposes. With limited exceptions, researchers may not disclose names, information or documents containing information you give for study purposes. This Certificate does not expire.

However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Also, we may have to release your information if the organization that is funding this study, [*Funding Agency*], requests the information, or if the FDA, EMA or other regulatory body tells us to release this information. This Certificate does not prevent you or your partner from releasing information about yourselves and your participation in the study.

RESEARCH-RELATED INJURY
It is unlikely that you will be injured as a result of study participation. The U.S. NIH does not have a mechanism to pay money or give other forms of financial compensation for research-related injuries. You do not give up any legal rights by signing this consent form. ***[Sites to replace with their site-specific research-related injury institutional policy if they already provide clinical trials insurance:]*** If you are injured as a result of study participation, the ***[INSTITUTION]*** will give you immediate necessary treatment for your injuries. You ***[WILL/WILL NOT]*** have to pay for this treatment. If you need additional treatment for your injuries, the site staff will refer you for ongoing care at the site or at another nearby facility. You ***[WILL/WILL NOT]*** have to pay for this additional treatment.

CLINICALTRIALS.GOV
A description of this research study will be available on http://www.ClinicalTrials.gov. This web site will not include information that can identify you or your partner. At most, the web site will include a summary of the results. You can search this web site at any time.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER
Taking part in this study is completely voluntary. You and your partner may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled. If you want the results of the study after the study is over, let the study staff members know.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact ***[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]*** at ***[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]***.

If you have questions about your rights as a research participant, you should contact:***[INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]*** at ***[INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER]***.

SIGNATURES- VOLUNTARY CONSENT

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC]:

If you have read this consent form (or had it read and explained to you) and if you understand the information and voluntarily agree to take part in the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

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