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# A Double-Blind, Single Center, Randomized 3-way Crossover Trial to Determine Pleasure for Fitted, Thin and Standard Condoms, and to Assess Clinical Failure for Vaginal and Anal Sex

**Short Title:**

Condom – Performance in a Longitudinal Enhanced ASsessment of UseR Experiences (C-PLEASURE)


**Investigators:**

Patrick Sullivan, DVM, PhD

Michael Cecil, MD

Eli Rosenberg, PhD

Aaron Siegler, PhD



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## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AE | Adverse Event |
| CDC | Centers for Disease Control and Prevention |
| CDMS | Clinical Data Management System |
| CFR | U.S. Code of Federal Regulations |
| CITI | Collaborative Institutional Training Initiative |
| CLIA | Clinical Laboratory Improvement Amendments |
| eCRF | Electronic Case Report Form |
| FDA | U.S. Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardization |
| LGBT | Lesbian, Gay, Bisexual, and Transgender |
| MSA | Metropolitan Statistical Area |
| MSM | Men who have sex with men |
| MSW | Men who have sex with women |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| OSHA | Occupational Safety and Health Administration |
| PrEP | Pre-Exposure Prophylaxis |
| RT-PCR | Reverse Transcription-Polymerase Chain Reaction |
| STI | Sexually Transmitted Infection |
| UNFPA | United Nations Population Fund |
| USAID | United States Agency for International Development |

## PROTOCOL TEAM ROSTER

**Lead Investigators**

**Patrick Sullivan, DVM, PhD**
Professor, Department of Epidemiology
Rollins School of Public Health
1518 Clifton Road NE
Atlanta, Georgia 30322
Phone: 404-727-2038
Email: pssulli@emory.edu

**Michael Cecil, MD**
CEO
TheyFit, LLC
4140 Tate Street NE
Covington, GA 30014
Phone: 404-441-4435
Email: mpcecil@earthlink.net

**Eli Rosenberg, PhD**
Assistant Professor, Department of Epidemiology
Rollins School of Public Health
Emory University
1518 Clifton Rd NE
Atlanta, Georgia 30322
Phone: 404-712-8897
E-mail: erose2@emory.edu

**Aaron Siegler, PhD**
Assistant Professor, Department of Epidemiology
Rollins School of Public Health
1518 Clifton Road NE
Atlanta, Georgia 30322
Phone: 404-712-9733
Email: asiegle@emory.edu

**Colleen Kelley, MD**
Assistant Professor of Medicine, Division of Infectious Disease
Rollins School of Public Health
1518 Clifton Road NE
Atlanta, Georgia 30322
Phone: 404-712-1823
Email: cfkelle@emory.edu

**Clinical Laboratory**

**Quest Diagnostics**
2801 N Decatur Rd Suite 185
Decatur, Georgia 30033-5924

**Kraft Labs**
101 Woodruff Circle, Room 7007
Atlanta, Georgia 30322

## 1. INTRODUCTION

Male condoms effectively prevent human immunodeficiency virus (HIV) and sexually transmitted infection (STI) transmission, but are underutilized in large part to due to reduced experiences of pleasure. Annually, in the United States, there are approximately 20 million incident cases of STIs,[1] and over 50,000 new HIV infections.[2] The vast majority of new HIV infections (92%) were acquired through vaginal or anal sex, with anal sex alone accounting for more than two-thirds of new infections.[3] The highest priority for any condom promotion effort is to change factors that lead to condom nonuse.[4] Perhaps the most cited and universal reported rationale for not using condoms is the perception that condoms decrease sexual pleasure.[5-8]

Nearly half of men report poor condom fit; these men are less likely to use condoms. Estimates indicate a range of 35-50% of condom users report poor condom fit.[5,9-11] Studies have found that men who have sex with men (MSM) who either perceive condoms as too tight[12] or report larger than average penis size[9] were more likely to report unprotected anal sex. One reason for this is that men who perceive poor condom fit are more likely to report reduced pleasure due to condom use.[5,11]

The premise of fitted condoms is that better fitting condoms may enhance perceptions of pleasure or overall preference for men considering condom use. We believe that there are two biologically plausible hypotheses for this premise. First, men reporting larger penile size are more likely to describe standard condoms as feeling "tight",[10,12] and this tightness could lead to decreased perceptions of pleasure. Second, men who report smaller penis size are more likely to describe condoms as feeling "loose",[10] and this additional slack (circumference) or rolled (shaft) latex could lead to decreased perceptions of pleasure. There is a scientific need to explore the relationship between fitted condoms and pleasure.

Research is also needed to better understand condom performance for anal sex applications. MSM are estimated to account for nearly two out of every three new HIV infections in the United States,[13] and are the only group with increasing HIV incidence.[14] Previous estimates of clinical condom failure (slippage or breakage) during anal sex have often not measured failure at the event level. Two studies have assessed clinical condom failure prospectively at the event level, with clinical failure reported in 6.3%[15] and 6.9%[16] of anal sex acts. One study found that fitted condoms had lower breakage failure rates than standard condoms for anal sex.[16]

For this study, we will use a mobile-optimized, web-based home daily coital log that allows for event level measurement. We anticipate that use of this system will decrease recall bias, avoiding possible limitations of paper-based recall systems that do not have time stamping to accurately determine the time of form completion. We anticipate that, with the use of a system that decreases recall bias, we may have higher sensitivity to detect clinical failure across all study conditions (fitted, thin and standard).

For purposes of this study, a "standard" condom is defined by dimensions commonly sourced by the United Nations Population Fund (UNFPA) and United States Agency for International Development (USAID), which procures the majority of the world's condoms (Steven Hamel, BS, email communication, June 23, 2015). These dimensions are 185mm ± 10mm length, 53mm

± 2mm width, and 70 microns ± 10 microns thick (Lai Peng Lim, BS, email communication, June 23, 2015). "Thin" condoms for this study will be of identical width and length to "standard", but 50 microns ± 5 microns thick. Fitted condoms will be produced in a range of sizes (uploaded to eIRB) with thickness of 70 microns ± 10 microns, with a participant's fitted size as determined by their use of a fitting system consisting of a paper template graduated with non-sequential numbering and lettering (uploaded to eIRB). All condoms will be manufactured by Karex International. Condoms will be manufactured using the same latex formulation and silicone lubricants (approximately 400mg per condom), and with similar parallel wall designs.

## 2. AIMS

The study will enroll 252 MSM and 252 men who sex with women (MSW) into a double-blind, three-way randomized crossover trial with conditions of fitted, thin, and standard condoms. For the MSM arm of the trial we will assess outcomes based on anal sex, and for the MSW we will assess outcomes based on vaginal sex. We are conducting this trial with the objectives of (for Aims 1 and 2) establishing label indications for pleasure and patient preference for fitted condoms, (for Aim 3) establishing a label indication for anal sex for fitted, thin, and standard condoms, and (for Aim 4) establishing a label indication for decreased clinical failure of fitted condoms for anal sex.

**Aim 1.** To compare fitted condoms with standard condoms regarding levels of reported pleasure as determined by rating per condom use event.
**Hypothesis 1.** Fitted condoms will have higher pleasure ratings than standard condoms.
**Hypothesis Rationale 1.** There is biological plausibility and published data indicating that condoms fitted to penile dimensions could improve perceptions of pleasure.

**Aim 2.** To compare fitted condoms with standard condoms regarding preference as determined by ranking of the two conditions at the study conclusion.
**Hypothesis 2.** More participants will prefer fitted condoms than standard condoms.
**Hypothesis Rationale 2.** There is biological plausibility and published data indicating that condoms fitted to penile dimensions could improve perceptions of pleasure.

**Aim 3.** To assess for fitted, thin, and standard condoms the total clinical failure rate of each type of condom for anal sex among MSM relative to a cut-point to be determined by the United States Food and Drug Administration (FDA).
**Hypothesis 3.** All condom conditions will have clinical failure point estimates less than a cut-point level of acceptable clinical failure, with the cut-point to be determined by the FDA.
**Hypothesis Rationale 3.** Condoms are currently recommended for anal sex use for the prevention of STI and HIV by the U.S. Centers for Disease Control and Prevention (CDC), the United Nations, and the World Health Organization.

**Aim 4.** To compare fitted condoms with standard condoms regarding total clinical failure for anal sex among MSM.
**Hypothesis 4.** Fitted condoms will have a lower total clinical failure rate than standard condoms for anal sex among MSM.

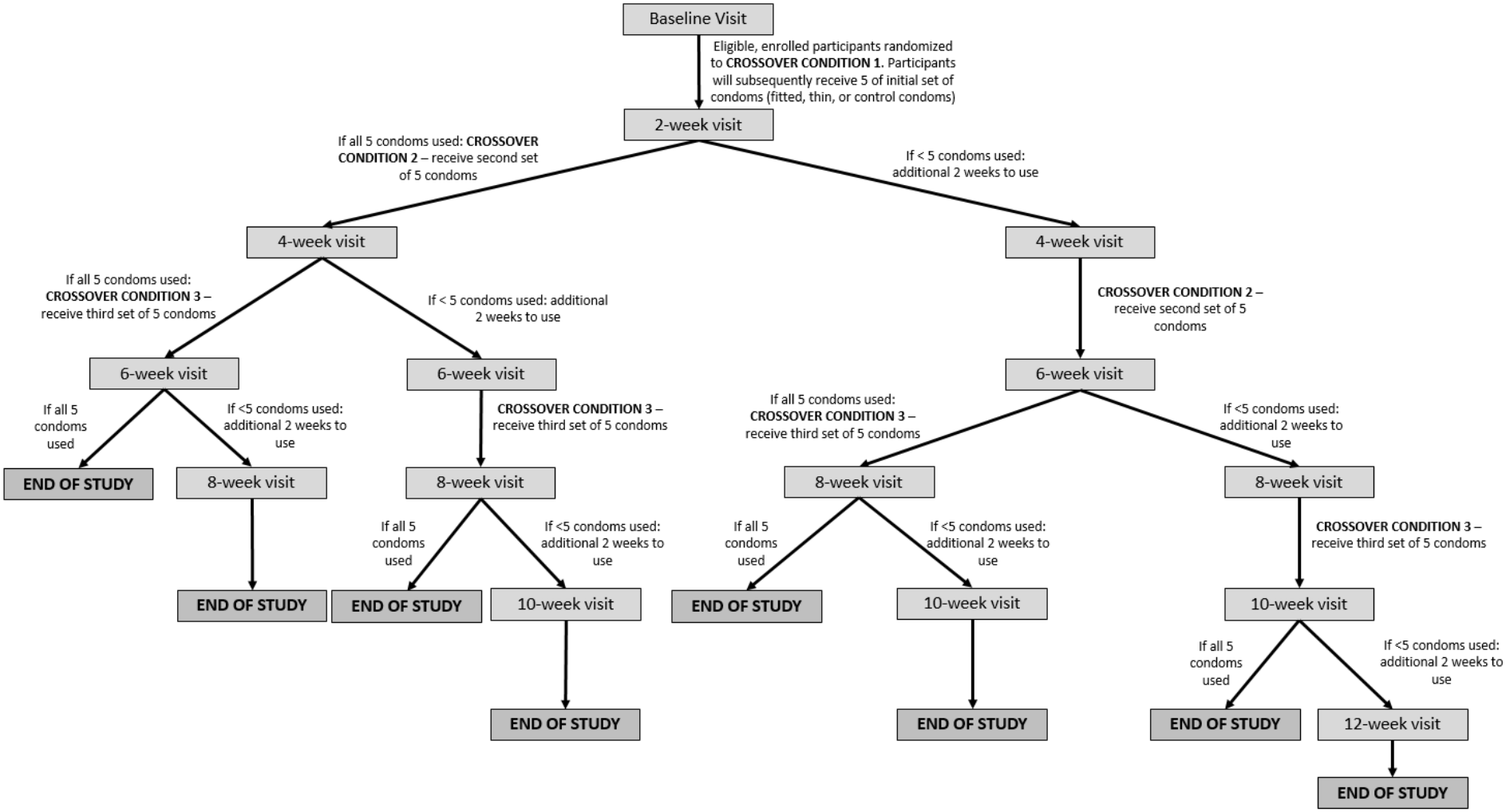
**Hypothesis Rationale 4.** Biological plausibility and published data from a prospective, event-level assessment of clinical failure indicate that fitted condoms may have superior clinical performance for anal sex.[16]

## 3. STUDY OVERVIEW

### 3.0 Study Design

This study is a randomized crossover trial of 252 HIV-negative MSM and 252 HIV-negative MSW. Every participant in the trial will receive a batch of five fitted condoms, a batch of five thin condoms, and a batch of five standard condoms over a series of study visits. We will randomize the order in which fitted, thin, and standard condoms will be distributed. Event-level data based on a home coital log will be collected regarding pleasure and total clinical failure (Aims 1, 3 and 4), and data regarding overall condom preference (Aim 2) will be collected at the final study visit. All participants will complete an informed consent form (ICF) (uploaded to eIRB). Eligibility assessment will include HIV testing and symptomatic STI and acute HIV screening. The order in which study condoms will be received will be determined by permuted block randomization. Participants will be provided access to a mobile-optimized, web-based home coital log diary that is 21 U.S. Code of Federal Regulations (CFR) Part 11 compliant, in which participants will document each instance of study condom use as soon as possible following any vaginal or anal sex acts. Log entries will include assessment of pleasure and clinical failure, as well as other pertinent information such as substance use, lubricant, and any potential events including errors during application. Participants will be enrolled over a period of approximately 6-12 months, depending on the speed of recruitment. Each participant will be followed for six to twelve weeks after enrollment, depending on their use of study condoms in each two-week period between study visits (Figure 1). Participants will return for a follow-up visit two weeks after baseline. Participants will be given up to four weeks to use each study condom set; after 4 weeks with a set of condoms, participants will be automatically crossed over into the next study condition. If all condoms are used within the first two weeks, participants will crossover to the next randomized study condoms at that point (Figure 1). If participants do not use all study condoms in the first two weeks after the have been dispensed, participants will be given a second 2-week period to use the batch of condoms. Throughout the duration of study participation, coital logs will be completed.

**Figure 1. Visit schedule**



### 3.1 Study Timeline

We estimate the study will start enrolling participants in March 2016, although it may start at an earlier time point. Recruitment will last until 252 eligible MSM and 252 eligible MSW are recruited, approximately 6-12 months. As eligible participants are recruited, they will be scheduled for a baseline screening and enrollment visit. The research team will hold study research events as needed upon study launch. Participants will be able to select a preferred event day and time to complete study visits.

| Q4 | | | Q1 | | | Q2 | | | Q3 | | | Q4 | | | Q1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| M10 | M11 | M12 | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M10 | M11 | M12 | M1 | M2 | M3 |
| Recruitment | | | | | | Recruitment and study visits | | | | | | Enrolled participant study visits, no further recruitment | | | Results analysis and dissemination | | |

### 3.2 Study Locations

In order to allow a diverse group of participants to take part and remain in this study, we will select study sites in central areas of Atlanta that are easily accessible both by public transit and by private car with ample parking. Possible sites at which participants will be seen include:

- **Rollins School of Public Health, Emory University**
  1518 Clifton Road NE
  Atlanta, GA 30329
- **Wesley Woods Health Center, Emory University**
  1841 Clifton Road NE
  Atlanta, GA 30329

## 4. STUDY POPULATION

### 4.0 Sample

Eligible participants will be HIV-negative, aged 18-54 years, live in the Atlanta metro area, and be currently sexually active. We will enroll 252 HIV-negative MSM and 252 HIV-negative MSW. All 504 enrolled participants will be eligible to attend at least four, and up to seven study visits. For purposes of study assignment, men entered into the MSM arm will be defined as a man who intends to only have sex with only other men in the next 12 weeks and men entered into the MSW arm will be defined as a man who intends to only have sex with women in the next 12 weeks. Men who intend to have sex with both men and women in the next 12 weeks will not be included in the sample. Due to potential differences in proficiency with condom use for anal and vaginal sex, anal sex acts reported by men in the MSW arm will be excluded from the analyses.

*Vulnerable populations*: The study will not enroll children, prisoners, pregnant women or any other vulnerable populations.

## 4.1 Participant Inclusion and Exclusion Criteria

### 4.1.1 Inclusion criteria

Participants must meet all of the inclusion criteria to enter into the study.

The entry inclusion criteria are:

1. Age 18-54
2. Lives in or near Atlanta metropolitan statistical area (MSA)
3. Plans to be in Atlanta for the majority of the 12 weeks of enrollment
4. Able to independently complete survey instruments in English
5. Male sex at birth
6. Currently identifies as male
7. For MSM, self-report to have only had sex with men in the past four weeks
8. For MSW, self-report to have only had sex with women in the past four weeks
9. Self-report no transgender sex partners in the past four weeks
10. Self-report at least 1 anal (MSM) or vaginal (MSW) sex act in the past four weeks
11. For MSM, self-report intends to have sex only with men in the next 12 weeks
12. For MSW, self-report intends to have sex only with women in the next 12 weeks
13. For MSM, self-reports an insertive role in the past four weeks or willing to be the insertive partner when using study condoms for anal sex
14. Willing and able to have sex using a latex condom provided by study
15. For MSW, report that current partner is not currently pregnant
16. For MSW, report that current partner does not desire to become pregnant currently or in the next 12 weeks
17. Consistently able to maintain an erection while using condoms
18. Not allergic to latex
19. Current partner(s) not allergic to latex
20. No genital piercings
21. For MSW, female current partner(s) does (do) not have vaginal piercings
22. For MSM, male current partner(s) does (do) not have anal piercings
23. Current partner(s) not known to be HIV-positive
24. Self-report absence of sexually transmitted infections, including HIV
25. Negative HIV rapid test result or confirmed negative HIV test at baseline
26. Willing to provide at least two means of contact
27. Willing to only use lubricant provided by study
28. Not allergic to water-based lubricant
29. Current partner(s) not allergic to water-based lubricant
30. Willing to use a fitting tool to determine penile dimensions

All participants must provide written informed consent to participate in the study.

### 4.1.2 Exclusion criteria

Potential participants meeting any of the exclusion criteria at baseline will be excluded from participating in the study.

The exclusion criteria for the study are:

1. <18 years of age or >54 years of age
2. Does not live in or near Atlanta MSA
3. Does not plan to be in Atlanta for the majority of the 12 weeks of enrollment
4. Unable to independently complete survey instruments in English
5. Not male sex at birth
6. Does not currently identify as male
7. Self-report to have had sex with both men and women in the past four weeks
8. Self-report transgender sex partners in the past four weeks
9. Self-report no anal (MSM) or vaginal (MSW) sex act in the past four weeks
10. Self-report intends to have sex with both men and women in the next 12 weeks
11. Never the insertive partner for anal sex or not willing to be the insertive partner when using study condoms for anal sex
12. Not willing or unable to have sex using a latex condom provided by study
13. Plans to not have sex in the next four weeks
14. For MSW, report that current partner is currently pregnant
15. For MSW, report that current partner desires to become pregnant currently or in the next 12 weeks
16. Unable to consistently maintain an erection while using condoms
17. Allergic to latex
18. Current partner(s) allergic to latex
19. Genital piercings
20. For MSW, female current partner(s) has (have) vaginal piercings
21. For MSM, male current partner(s) has (have) anal piercings
22. Current partner(s) known to be HIV-positive
23. Self-report presence of sexually transmitted infections, including HIV
24. Confirmed HIV positive at baseline
25. Not willing to provide at least two means of contact
26. Not willing to only use lubricant provided by study
27. Allergic to water-based lubricant
28. Current partner(s) allergic to water-based lubricant
29. Not willing to use a fitting tool to determine penile dimensions

## 4.2 Recruitment Procedures

### 4.2.1 Primary recruitment method

The primary method of recruitment for both MSM and MSW will be venue-based, face-to-face recruitment that will take place in a variety of public and private venues in Atlanta where men congregate. These will include bars, dance clubs, retail stores, street corners, restaurants, churches, college campuses, and other public places.

#### *4.2.1.1 Primary recruitment procedures*

All recruiters will be trained in the Collaborative Institutional Training Initiative (CITI)'s ethical conduct of research. At the recruitment event, trained recruiters will approach potential participants, obtain permission to screen, and administer

a brief recruitment script and set of screening questions using a handheld device (recruitment materials uploaded to eIRB).

Eligibility will be assessed in three stages, because of the detail and sensitivity of some of the eligibility criteria. The first stage will be during this recruitment event, where we will screen on a subset of the eligibility criteria, such as age and recent sexual activity. Potential participants meeting these criteria will be asked to provide first name, first, middle (if applicable), and last initial and contact info (email address and phone numbers).

Recruiters will hand out study contact cards and commercially-available condoms (not fitted) and lubricant to eligible or interested participants. We will provide commercially-available (not fitted) condoms and lubricant to all participants, regardless of their participation in the screener or their study eligibility.

Every potential participant providing this contact information will be sent an electronic consent form that will indicate willingness to receive a full eligibility screening. Potential participants affirmatively completing this electronic consent will be contacted and screened for the full list of eligibility criteria. Those who indicate they are not willing to consent will not be contacted, and their information will be deleted from the recruitment database. Those determined to pass the second stage of eligibility criteria will be mailed or emailed a fitting tool and scheduled for a study visit (which will include a further consent process, detailed below).

Potential participants providing contact information but who have not completed the electronic consent process will be contacted via phone to assess their interest in the study. These participants will be given the option of completing a verbal consent process for eligibility screening over the phone. Potential participants who complete the verbal consent process will be screened for the second stage of eligibility criteria, and those eligible will be scheduled for a study visit. We have uploaded to eIRB versions of the verbal and electronic screening consent.

Eligible participants will be given the option to determine their fitted condom size prior to attending their baseline visit, using the fitting tool sent following the phone screening and an electronic demonstration video.

Scheduling and phone scripts are described in more detail in section 7.1.1 and are uploaded to eIRB.

#### *4.2.1.2 Description of recruitment contacts*

The recruiter will walk up to potential participants and introduce the project according to a recruitment script. We will then perform the first stage of eligibility assessment. MSM and MSW who are not eligible for reasons other

than insertive partner status will be thanked for their time, but no identifying information will be collected. MSM who are not eligible because they are not the insertive partner may be asked to give a contact card to their partner, if applicable. Those eligible will be asked to provide a first name, first, middle (if applicable) and last initial, email address, and phone number(s) if they are willing to be contacted for further screening and potentially scheduled for an informed consent and baseline visit. Responses to screening questions will not be saved in the study database, with all eligibility criteria to be re-assessed and entered into the study database at the baseline visit (the third screening stage). The following script is one example of the type of communication that will be used to initiate contact in the field:
"Hi, my name is [name] and I am working with Emory University on a men's health study. Can I ask you a few questions to see if you are eligible to participate?"

### 4.2.2 Secondary recruitment methods

If primary recruitment methods do not identify a sufficient number of either MSM or MSW, we will incorporate secondary recruitment methods, which may include (1) flyers and paid advertisements, (2) recruitment from previous studies, (3) recruitment through female partners or receptive MSM, and (4) recruitment through referrals

#### *4.2.2.1 Flyers and paid advertisements*

Based on recruitment progress, and counts of MSM and MSW recruited, we may supplement primary recruitment using flyers and paid advertisements targeting the study population of interest. We may post flyers advertising the study in venues that men frequent, such as community and clinical spaces, colleges and universities (e.g., cafes, clubs, bars/restaurants, gyms, HIV/STI testing facilities, doctors' offices, and sex shops). We may also create paid advertisements in popular social networking sites including facebook.com, twitter.com, other gay-friendly sites like scruff.com, and local news and culture sites like ctatl.com. Example advertisements are uploaded to eIRB.

#### *4.2.2.2 Recruitment from previous studies*

We may recruit participants, who have consented to be contacted, from previous research projects conducted by our team in Atlanta (NIH study number: R01MH085600, R43HD078154, R01HD067111).

#### *4.2.2.3 Recruitment through partners*

We may also perform venue-based or online recruitment through female partners of MSW and through receptive partners of MSM. MSM who are ineligible because they are receptive will be asked if they have a partner. If they do have a partner, they will be given a study contact card in case their partner would like to participate. Individuals who are ineligible through online recruitment may be asked to share the survey link with their male partner. We

may also have recruiters approach women and recruit their male partners through a series of questions.

#### *4.2.2.4 Recruitment through referrals*

Participants may be asked to provide a referral code to up to three peers. Peers who receive the code and visit the link will be given the opportunity to take an online eligibility screener and consent to be screened on the phone. Study staff will contact eligible and electronically consented individuals and complete the second stage of eligibility screening on the phone. Those eligible will be scheduled for a study visit.

### 4.3 Participant Retention

Once a participant enrolls in the study, study staff will seek to retain the participant throughout the follow-up period in order to minimize possible bias associated with loss-to-follow-up. Study staff will be responsible for developing and implementing standard operating procedures to target this goal. Components of such procedures include:

- An explanation of the study and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Collection of detailed contact information at the study baseline enrollment visit, and active review and updating of this information at each subsequent visit.
- Use of daily reminder mechanisms, such as SMS or email reminders, to complete coital log entries for each study condom use.
- Study staff follow-up after unanswered daily reminders.
- Use of SMS, telephone, or email reminder mechanisms prior to scheduled visits.
- Immediate follow-up on missed visits, with rapid rescheduling.
- Monthly attempts to reengage participants who have been unresponsive to scheduling attempts through the duration of the study.
- To reduce the burden of study visit attendance on participants who do not own a vehicle, we will make available prepaid single-ride MARTA cards or prepaid fare for a car service for transit to study visits.

### 4.4 Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The study investigators also may withdraw participants from the study in order to protect participant or staff safety. Study staff will record the reasons for all withdrawals or holds from the study on a Study Stop Form in the participants' study records. Study stoppage may occur for the following reasons:

- Participants who self-report symptoms of STIs (described in more detail in section 7.1.2.2) will be referred to AID Atlanta for testing, but will be study stopped and will not attend follow-up visits.
- Participants who: (a) report that their current partner(s) is HIV-positive; (b) that they have had sex with someone in the past 30 days who is HIV-positive and plan to have sex with that partner again; or (c) add a new partner in the coital log who is HIV-positive

during the study, will be study stopped and given information on pre-exposure prophylaxis (PrEP).
- Participants also may be withdrawn if the study is terminated prior to its planned end date.

Participants may be temporarily held from the study for the following reasons:

- Participants who have had unprotected anal sex with a man OR injected a substance not prescribed to them in the past 30 days AND self-report symptoms of acute HIV, such as fever over 100°F, at baseline or follow-up visits will be paused until a viral load test is performed. Participants will be study stopped if they have a detectable viral load; participants can resume study visits if their viral load is undetectable.
- Participants with a preliminary positive rapid HIV test at baseline will be paused until results of a confirmatory test are received. Participants will be study stopped if they are confirmed to be HIV positive; confirmed HIV negative participants will be asked to return to complete their baseline visit.
- Participants experiencing discomfort or issues related to the study condoms or lubricant will be paused until the study physician can assess the severity of issues. Participants will be study stopped if the physician determines it is in the participant's best interest to discontinue participation in the study.

## 5. STUDY PRODUCT

### 5.0 TheyFit Condom

TheyFit, LLC manufactures 56 condom sizes based on combinations of length (approximately 10 mm increments) and circumference (approximately 2 mm increments). To determine appropriate condom size, TheyFit, LLC developed a trademarked fitting tool. This tool is a paper template graduated with non-sequential numbering and lettering for maximum privacy. The FDA has accepted the sizing device as an instrument to determine fitted condom size. All references to "TheyFit" will be removed from the fitting tool and from all other study components. The study will use the full range of the 56 TheyFit, condom sizes cleared by the FDA. TheyFit condoms will be manufactured by Karex.

### 5.1 Thin Condom

Thin condoms, as defined in section 1.1, were selected as an additional study condom because they are widely sold condoms in the United States and because of the general perception that are more pleasurable to use than standard condoms. Thin condoms will be manufactured by Karex.

### 5.2 Standard Condom

Standard condoms, as defined in section 1.1, were selected as the control because they are the most widely used condoms internationally due to their use by programs distributing condoms, such as USAID (Steven Hamel, BS, email communication, June 23, 2015). Standard condoms will be manufactured by Karex.

### 5.3 Lubricant

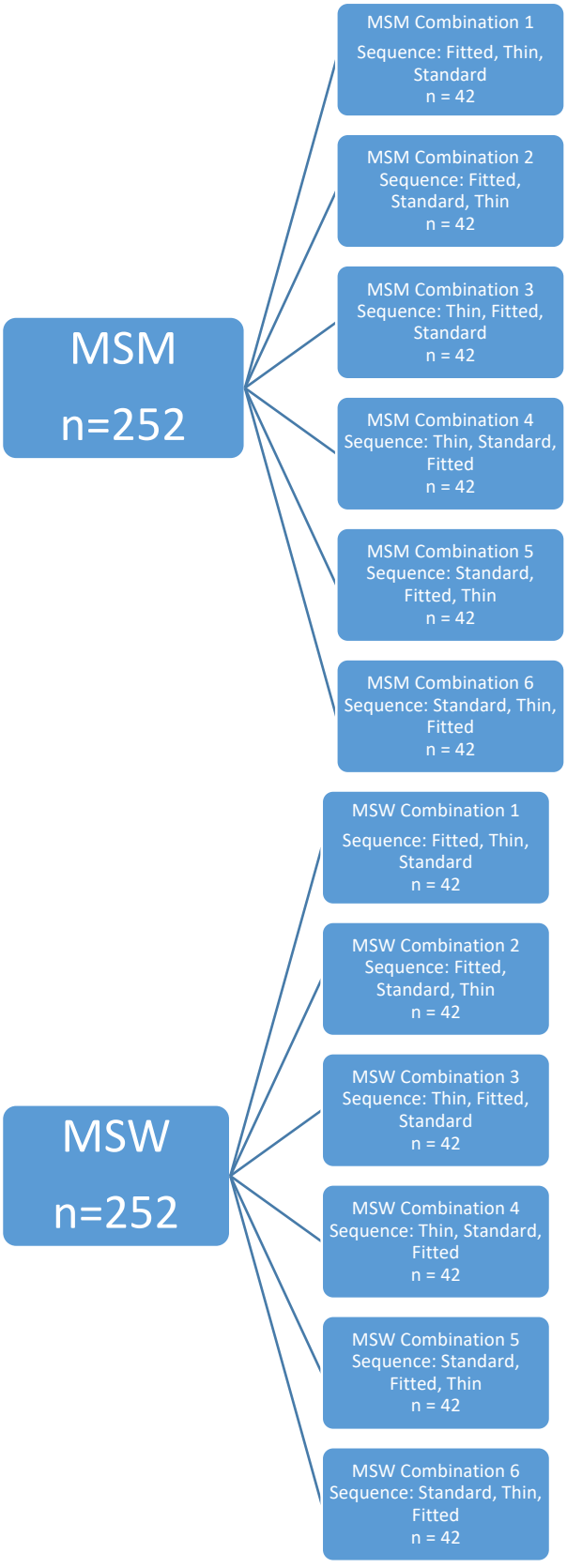
Study staff will provide participants with two packets per condom of 10ml commercially available condom-compatible water-based lubricants. Participants will be instructed not to use any other lubricants when using study condoms. MSM will be instructed to use lubricant with all anal sex acts. Coital log entries indicating incorrect use of lubricant will be excluded from clinical failure analyses (Aims 3 and 4). This includes use of non-study lubricant, use of lubricant inside the condom, and absence of lubricant use for anal sex.

## 6. TRIAL DESIGN

### 6.0 Study Arms

The study will have two arms: 252 eligible MSM and 252 eligible MSW. Within each study population, we will randomly assign the sequence in which study condoms (fitted, thin, and standard) are received.

**Figure 2. Study arms and crossover condition combinations**



### 6.1 Randomization

Eligible and consented study participants who complete their fitted condom self-measurement will be randomized to one of six crossover condition orders that balance the allocation of conditions (Table 1). The randomization sequence lists will be developed as follows. Within each study stratum (MSM or MSW), an unblinded data coordinator will develop permuted block randomization sequences in our electronic database, Dacima (see section 12.0 for more detail). The block sizes will be randomly chosen (e.g., 6, 12). These randomization sequences will be stored in Dacima. Following successful completion of baseline study visit procedures and self-measurement for fitted condoms, the participant will be automatically randomized by being assigned the next available crossover condition in the sequence within that participant's stratum. Dacima will then indicate to study staff which crossover condition to distribute at the baseline visit (or to mail if sizing occurred at home after the baseline visit) and appropriate subsequent study visits.

**Table 1. Randomized crossover orders**

| | Crossover Condition | | |
|---|---|---|---|
| Combination | 1 | 2 | 3 |
| 1 | Fitted | Thin | Standard |
| 2 | Fitted | Standard | Thin |
| 3 | Thin | Fitted | Standard |
| 4 | Thin | Standard | Fitted |
| 5 | Standard | Fitted | Thin |
| 6 | Standard | Thin | Fitted |

### 6.2 Blinding Procedures

In this closed label, double-blind trial, study condoms will be manufactured in plain foil packaging, with identifying two-digit random codes printed on each foil. Thin condoms will have a two-digit code, standard condoms will have a two-digit code, and each fitted condom size will have a random two-digit code to maintain blinding. Unblinded study staff will separate each condom type into different colored bags to allow for participants and study event staff to easily discriminate between the condom types. The randomization codes will be presented to study staff in a manner that supports blinding, using the color of the study condition to identify the condom to be distributed to a participant.

Blinding of study staff will be role-based. The study statistician and the principal investigator, who are responsible for analyses and reporting results to FDA, will be blinded until after the initial analysis of study results has been reported to FDA. Participants will also be blinded in order to minimize bias. The different condom types were matched to three different colors. These colors will be used to guide the process of condom distribution in the study. The colors, rather than the fitted, thin, and standard condom types, were entered into Dacima. Study staff who are not involved in the assessment of outcomes or analyses may be unblinded as needed to dispense the appropriate condoms to participants, but will be trained in how to interact with blinded participants without disclosing allocations or otherwise influencing participants.

We recognize an inherent limitation to the blinding scheme in that some participants may be able to detect their assigned condition. In particular, some participants may be able to identify fitted condoms due to potential size difference from standard condoms. Similarly, some participants may be able to detect a thin condom due to thickness difference from standard condoms. We will seek to mitigate this potential bias by recording the perceived study condom assigned, and assessing in secondary analyses whether participants who are able to detect their assigned study condition report differently on key outcomes than participants who are unaware of their study condition.

Based on previous trials, we expect possible adverse events (AE) to include symptomatic and asymptomatic STIs (particularly in area not covered by condom), acute HIV infection, discomfort or other issues related to the study condoms or lubricant, and pregnancy (for current partner of MSW) (described in Section 8.1.1).

If any adverse event occurs at a rate of 1.5 times greater than expected, the principal investigator will consider unblinding the study at the investigator level, in consultation with the study physician. Assuming that we will follow people on average for 10 weeks, we expect chlamydia and gonorrhea among MSW to occur among less than 0.5% of participants during the study period, based on 2013 surveillance data for men in Georgia.[17] Based on estimates from a previous study in Atlanta we expect urethral chlamydia and gonorrhea among MSM to occur among less than 1% of participants and rectal chlamydia and gonorrhea among MSM to occur among less than 4% of participants during the study period.[18]

Given that there is a 50-90% rate of acute symptoms among incident HIV infections[19] and an 11% incident rate of HIV observed among young black MSM in Atlanta,[20] we expect over the 6-10 week study period acute HIV infection among 1.3% of MSM participants. Because there are limited data available regarding incidence HIV rates among MSW in Atlanta, we estimate acute HIV infections to be one-fifth of that for MSM, or 0.25% of MSW participants.

Discomfort or other issues related to the study condoms or lubricant are expected to occur at a rate of 20% (Richard Crosby, PhD, email communication, August 11, 2015). Pregnancy for current partners of MSW is expected to occur among less than 4% of partners during the study period.[21] However, we expect 52% of MSW and their current partners will not be using condoms as the main form of birth control.[22]

### 6.3 Crossover Procedures

There will be three crossover conditions during this study. Each participant will be given five of each study condom set and will have up to four weeks to use all five condoms.

If five coital log events are recorded by the end of the two-week follow-up visit for any crossover condition, participants will be crossed over to the next crossover condition or determined to have completed the study (after completing five coital log events for the third study condom set). If five coital log events are not recorded by the end of the two-week follow-up, participants will be given another two weeks to use the study condoms in that

crossover condition. At the four-week follow-up for the first two crossover conditions, participants will be automatically crossed over to the next crossover condition. Participants will be automatically completed in the study after four weeks on the third crossover condition. The crossover procedures and possible crossover condition combinations are shown in Figures 1 and 2 and Table 1.

## 7. STUDY PROCEDURES

### 7.0 Visit Structure

Visual depictions of the baseline and follow-up visit structures are provided below.

**Figure 3. Baseline visit structure**

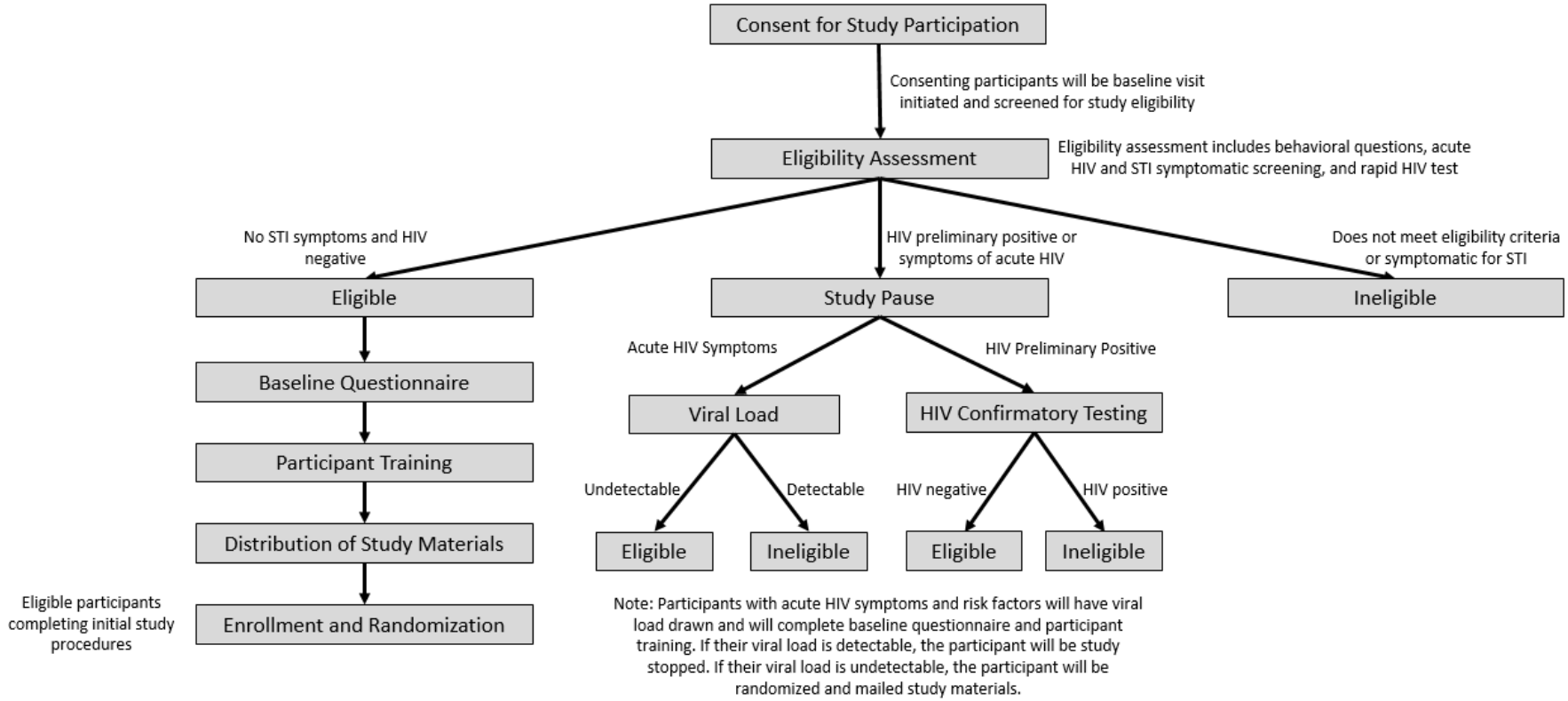
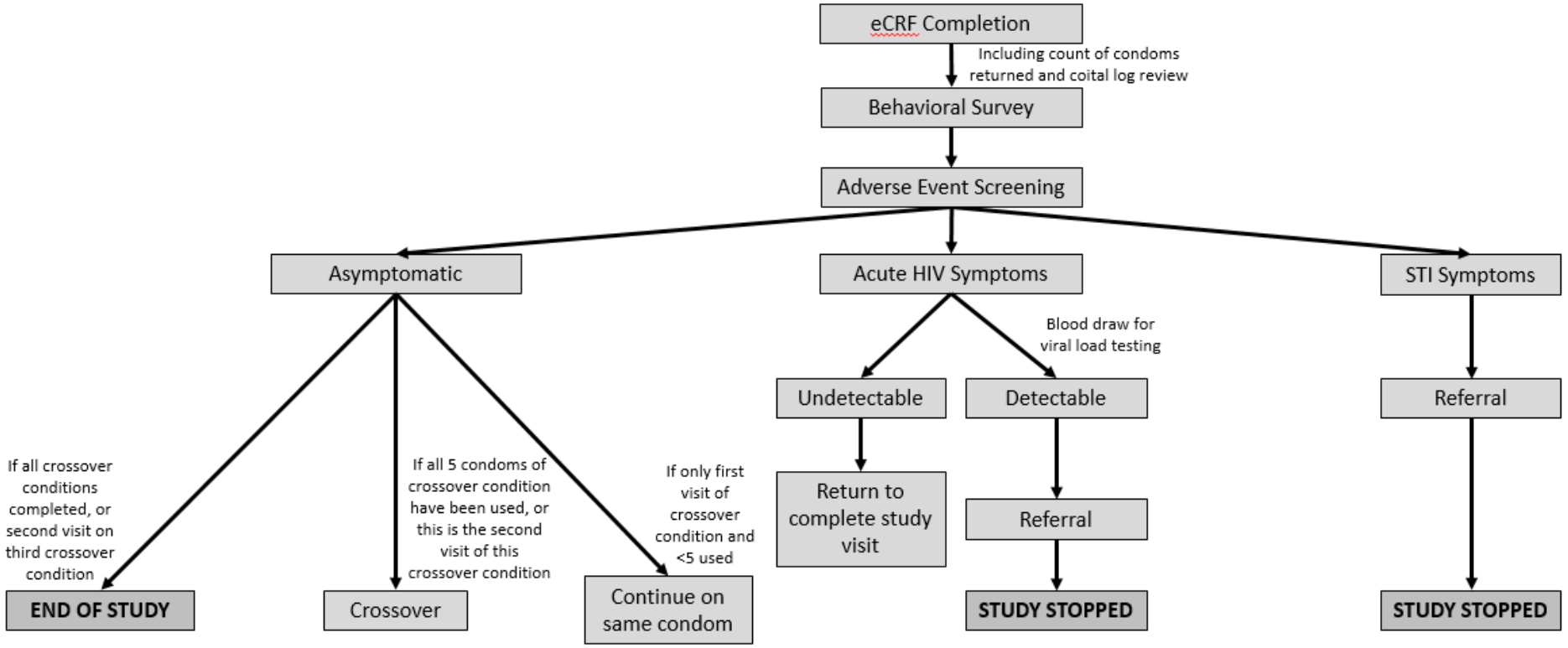


**Figure 4. Follow-up visit structure**



## 7.1 Visit Procedures

### 7.1.1 Scheduling

Using contact information gathered from primary or secondary recruitment methods, study staff will contact potential participants via phone or email. During the screening call, study staff will assess additional eligibility criteria. Eligible and interested participants will be scheduled for an enrollment (baseline) visit. See Figure 3 for a summary chart of the baseline visit.

### 7.1.2 Enrollment/Baseline Visit

#### *7.1.2.1 Consent for Study Participation*

- Upon arrival at the baseline visit, participants will be provided with the ICF for study participation. Each participant will be given a chance to review the consent document with and have any questions answered by study staff. Consenting participants and the witnessing study staff will sign the form. Participants will be given a copy of the consent for their own records.

#### *7.1.2.2 Eligibility Assessment*

- All consenting participants will be screened for eligibility.
- Study staff will complete an electronic Case Report Form (eCRF) to assess eligibility of participants.
- As part of the eligibility assessment, participants will be screened with an eCRF for symptoms of STIs and acute HIV infection (uploaded to eIRB).
    - If the participant self-reports symptoms of any STI, they will be referred to AID Atlanta for testing and treatment as needed. Participants symptomatic for STIs will receive their incentive for the visit and will be ineligible to continue in the prospective study.
    - If the participant has had unprotected anal sex with a man OR has injected a substance not prescribed to him in the past 30 days AND self-reports symptoms of acute HIV infection, blood will be drawn for HIV viral load. Participants being tested for acute HIV infection will continue with their baseline visit, but will not receive study condoms until their results are returned.
        - Once study staff receive their laboratory results, if the participant has no detectable viral load, the participant will be allowed to continue in the study: they will be randomized, shipped study condoms, and scheduled for their next follow-up visit.
        - If the participant has a viral load that indicates acute HIV infection, they will be actively linked to HIV care. Results will be returned by study staff experienced in HIV care linkage (scripts uploaded to eIRB). The participant will be study

stopped and will be ineligible to continue in the prospective study.

- Participants will be asked if they currently have a partner who is HIV positive. If a current partner is HIV-positive, the participant will be study stopped and will receive information on PrEP.

#### *7.1.2.3 HIV Testing*

- Eligible participants will receive HIV counseling, rapid testing, and results. Ineligible participants will be encouraged to receive HIV counseling and testing, but these services will not be required.
  - Participants will receive pre- and post-test counseling per CDC guidelines.[23]
  - HIV rapid testing will be conducted using the INSTI HIV-1 antibody test (described in section 11.0).
    - Participants with preliminary positive results will be scheduled to receive confirmatory testing at a private location of Emory's choosing. All preliminary positive results will be confirmed with a 4th generation immunoassay with reflex by a study laboratory per CDC guidelines.[24] Participants with preliminary positive rapid HIV test will receive their incentive and their study visit will end at this time.
    - The results of the confirmatory testing will be returned by study staff experienced in HIV care linkage (scripts uploaded to eIRB). Participants with confirmed HIV infection will be ineligible to continue in the prospective study.
    - Participants with two invalid INSTI tests or who are unable to provide enough blood for the INSTI test will be scheduled to receive confirmatory testing and will be paused from study participation until results are delivered.
    - Participants who are confirmed to be negative for HIV infection will be contacted to return to complete baseline visit procedures. Participants can be given a copy of their HIV rapid test result upon request (uploaded to eIRB).

#### *7.1.2.4 Baseline Questionnaire*

- Participants will complete a self-administered behavioral survey (uploaded to eIRB) on an electronic tablet or study computer including questions in the domains of:
  - Sexual history
  - Condom history
  - Sexual dysfunction
  - Condom slippage and breakage
  - Lubricant use
  - Therapeutic methods

- Condom fit and feel
- Condom perceptions
- Self-efficacy around condom use
- HIV and STI history
- Partner history
- Pleasure

#### *7.1.2.5 Participant Training*

Study staff will train all eligible participants regarding correct condom use and completion of coital logs. Participant training materials are uploaded to eIRB.

- Study staff will train participants in correct condom use based on a training module that comes from a CDC-determined Effective Behavioral Intervention (DEBI).[25]
    - The eight steps for condom success from the intervention include: putting the condom on before sex, opening the package without damaging the condom, finding the top of the condom, rolling it to the base of the penis, (as needed) adding water-based lubricant to the outside of the condom, wearing condom throughout entirety of sex act including ejaculation, holding the rim of the condom upon withdrawal, and avoiding spilling onto the genitals, mouth or rectum.
    - Study staff will instruct participants to use each condom for one sex act only. If they have multiple sex acts in a session, they should take the condom off between acts and use a second condom.
    - Study staff will instruct participants to only use condom-compatible lubricant provided by the study and to only apply lubricant to the exterior of the condom.
        - MSM will be instructed to use lubricant with all anal sex acts, MSW will be instructed to use lubricant as needed
        - Coital log entries indicating incorrect use of lubricant will be excluded from clinical failure analyses (Aims 3 and 4). This includes use of non-study lubricant, use of lubricant inside the condom, and absence of lubricant use for anal sex.
- Participants will also receive training on accessing and completing the home electronic coital log (uploaded to eIRB).
    - For participants without access to the internet and a functioning web browser at home, we will provide smartphones for use during the study.
    - Study staff will go through each question in the log with participants to clarify instructions and answer any questions.
    - Study staff will discuss when participants should complete the log (as soon as possible following intercourse) and how to access the log.

- Participants will be provided with an opportunity to personalize their username and their unique password used for both their login and electronic signature. This will also include information on how to come up with a memorable password and how to reset their username and password if either is forgotten.
- Participants will be asked what time of day they prefer for their daily coital log reminders, and this information will be entered into the scheduling system.

- Study staff will go over the visit schedule with participants.
- Participants will be instructed to return unused study condoms and any condoms that break (to be returned in study-provided biohazard bags) at their follow-up visit. The return and subsequent analysis of broken condoms will be conducted according to instructions detailed in Annex H of International Organization for Standardization (ISO) Guidance Document, ISO TC 157 N 770.[26]
    - Participants who did not determine their fitted condom size at home will receive information regarding determination of their fitted condom size. This information (video and text) will be identical to that which was received by participants who conducted the procedure prior to their visit. Participants will be asked to determine their fitted condom size at home within 2-5 days of the baseline visit.
    - All participants will enter their fitted condom size into a secure electronic form.

#### *7.1.2.6 Distribution of Study Materials*

- Study condoms will be provided to participants in batches of five. Each time a participant enters into a crossover condom condition, they will be given the batch of those five condoms, other batches will not be provided until the appropriate crossover time.
    - If we are out of stock of a certain size, participants will be given the next size up length or width.
- Participants will be provided study lubricant, printed study materials such as instructions for proper condom use, and a biohazard bag to return any broken condoms.

#### *7.1.2.7 Enrollment and Randomization*

- Eligible participants who have completed initial study procedures will be enrolled in the study.
- Participants will be randomized to a study arm, based on methodology specified in section 6.1, once they complete their fitted condom sizing.
    - Participants who choose to complete their fitted condom sizing at home after their baseline visit will be shipped their initial batch of condoms.

### 7.1.3 Follow-up Visits (Week 2, 4, 6, and if applicable, weeks 8, 10, and 12)

At the end of the participant's baseline visit, enrolled participants will be scheduled for follow-up visits at weeks two, four, and six. If the participant is unable to schedule all three visits at this time, or as conflicts arise, visits can be rescheduled as needed.

#### *7.1.3.1 Follow-up Preparation*

Prior to each visit, study staff will review electronic reports of the following for each scheduled participant:

- The number of condoms were recorded as used in the coital log in the last period
- The study visit number
- The cross-over schedule

#### *7.1.3.2 eCRF Completion and Coital Log Review*

- During each follow-up visit, study staff will perform a manual count of returned condoms and record this on an eCRF. The number of returned unused condoms will be compared to the number of study condom uses reported in the coital logs, and the number of returned broken condoms will be compared with the number of reported condom breakages.
    - If there are any discrepancies in the staff count and coital logs, study staff will query the participant about the discrepancy and work with the participant to resolve any discrepancies.
    - Discrepancies and how condoms were used that were not reported on coital logs (e.g. lost, MSW using condoms for anal sex) will be reported on an eCRF. If there are previously unreported events, participants will be given a chance to self-complete coital logs for up to two recent condom uses.
    - Study staff will replace any condoms that are lost on non-crossover visits.
- Study staff will review coital log entries with the participant during each visit. Study staff will confirm experiences in the coital log, such as confirming names and information of new partners encountered during the study.

#### *7.1.3.3 Visit Behavioral Survey*

- Participants will complete a self-administered behavioral survey (uploaded to eIRB) in the domains of:
    - Condom fit of the last study condom used
    - Perceived crossover condition
    - New sexual partners
- Prior to beginning the third crossover condition, participants will be asked their condom preference between the first two condom types.

#### *7.1.3.4 Visit Adverse Event Screening*

- Study staff will screen participants for symptoms of a STI or acute HIV infection using procedures from the baseline visit.
    - If the participant self-reports symptoms of any STI at follow-up, they will be referred to AID Atlanta for testing and treatment as needed. Participants symptomatic for STIs will receive their incentive for the visit and be study stopped. This will be recorded as an adverse event. See section 8.1.2 for more detail regarding adverse event reporting.
    - If the participant has had unprotected anal sex with a man OR has injected a substance not prescribed to him in the past 30 days AND self-reports symptoms of acute HIV infection, blood will be drawn for HIV viral load. Participants with acute HIV infection symptoms will receive their incentive and their study visit will end at this time.
        - Once study staff receive their laboratory results, if the participant has no detectable viral load, the participant will be allowed to return to complete their study visit. We will ship participants their next batch of condoms and schedule them for their next follow-up visit two weeks later.
        - If the participant has a viral load that indicates acute HIV infection, they will be actively linked to HIV care. Results will be returned by study staff experienced in HIV care linkage (scripts uploaded to eIRB). The participant will be study stopped and study staff will record this as an adverse event.
- Study staff will ask participants if they have experienced any discomfort or issues related to the study condoms. If they indicate any, participants may be asked to have a picture taken of the reaction for the study clinician's assessment. Depending on the severity of issues, as determined by the clinical judgment of the study physician, they may be study stopped.
- For MSW participants, study staff will ask whether their current partner is pregnant.
    - If that participant indicates that their partner is pregnant and the expected date of conception is during the study or unknown, their partner will be referred to the Grady Family Planning Wellness Clinic and study staff will record this as an adverse event.

### 7.1.4 Last Study Visit

- At their last study visit, participants will complete questions addressing overall condom preference (the study outcome for Aim 2). These pairwise comparison questions will assess preference for (1) fitted or standard condoms, (2) thin or standard condoms, and (3) fitted or thin condoms. Questions specific to the last study visit are uploaded to eIRB.

### 7.1.5 Reminders

- Participants will be instructed to complete a daily mobile-optimized, web-based home coital logs, and to complete a coital log entry as soon as possible after each study condom use.
- To assist participants in timely completion, participants will receive a daily email or text reminder with a link to the password-protected coital log if the participant has not completed a log in the last day
    - Participants will receive an initial reminder at the time of their choosing.
        - If the participant does not post a coital log entry within a specified time period after their initial reminder, they will receive a second reminder.
        - If the participant does not complete the daily coital log regularly, study staff will contact participants to encourage more consistent completion.
- Study staff will send participants appointment reminders using their preferred method of contact 3 days before, 1 day before, and the day of each study visit.
- If we find that participants have certain preferences regarding reminders, we may alter the frequency and method of reminders as needed.
- Example reminder scripts are uploaded to eIRB.

### 7.1.6 Coital Log

- Participants will be instructed to complete mobile-optimized, web-based home coital logs as soon as possible following any vaginal or anal sex acts. Participants can complete a coital log entry on a smartphone, tablet, or personal computer. For participants without access to web browsers at home, we will provide smartphones for their use during the study.
- The coital log will first ask whether the participant has had sex since their last coital log entry. If the participant has had sex, the coital log will explore event-level condom use factors including:
    - Sex event questions[26]
        - Date and time of day of condom use
        - Color of condom bag
        - Partner name
        - Lubricant use
        - Type of sex act
        - Quality of erection
        - Condom fit
        - Drug or alcohol use by participant or partner
    - Outcomes (described below in 7.3.4. Outcome Measures)
        - Clinical condom performance:
            - For breakage, we will assess when the breakage occurred.

        - For slippage, we will assess when the slippage occurred, whether they held onto the condom at the base of the penis while withdrawing, and whether the penis was still erect upon withdrawal.
    - Event-level sexual pleasure scale

## 7.2 Referral Procedures

### 7.2.1 Laboratory Referrals

All participants who have a preliminary positive HIV rapid test result, two invalid results, or are unable to provide enough blood for the rapid test at the enrollment visit will be scheduled to receive confirmatory testing at a private location of Emory's choosing. Confirmatory testing will include the participant having blood drawn for 4th generation immunoassay with reflex confirmatory testing. Participants testing preliminary positive will also be given the option to sign an assent form that would allow us to share their results directly with providers upon linkage to care. Laboratory testing will be done at a Clinical Laboratory Improvement Amendments (CLIA)-certified study laboratory. Results will be sent directly to study staff.

All participants who have had unprotected anal sex with a man OR have injected a substance not prescribed to him in the past 30 days AND self-report symptoms of acute HIV infection at their enrollment or follow-up visits will have blood drawn for viral load testing. Laboratory testing will be done at a CLIA-certified study laboratory, with results sent directly to study staff.

### 7.2.2 HIV Referrals

Once confirmatory results are received, study staff will contact the participant by phone. If the result is negative, the participant will be informed during the phone call. If the result is positive, the participant will be requested to come in for an additional visit, with the goal of having participants seen within 1-2 business days of their confirmed positive test result. Participants will be referred for individual assistance in accessing HIV care and treatment services at an appropriate organization experienced with HIV care such as AID Atlanta or Pride Medical in Atlanta, Georgia.

### 7.2.3 STI Referrals

All participants who are symptomatic for STIs at their enrollment or follow-up visits will be referred to either AID Atlanta or Pride Medical. AID Atlanta offers free STI screening and treatment, and we have successfully referred more than 190 men for STI treatment in previous studies (NIH study number: R01HD067111, R01MH085600).

### 7.2.4 Acute HIV Referrals

Once results are received, study staff will contact the participant by phone. Those with detectable viral load will be brought in for a visit, targeting within 24 hours of receiving a positive results. Participants at the visit will receive counseling regarding the infectiousness of the acute period, and the need to be particularly cautious. The

participants will be referred to appropriate care for acute infection. If participant has no detectable viral load, we will seek to reschedule their study visit to complete study procedures.

#### 7.2.5 Reactions/Side Effects to Condoms

Study staff will consult with an independent physician regarding the severity of any reactions or side effects to the study condoms. As appropriate, participants will be referred to AID Atlanta and study stopped.

#### 7.2.6 Pregnancy

All participants who report that their current partner is pregnant or may be pregnant will be referred to the Grady Family Planning Wellness Clinic.

#### 7.2.7 Condom Failure Referrals

Participants who report condom slippage or breakage in electronic coital log entries will receive an email with resources for HIV and STI testing, plan B, and non-occupational post-exposure prophylaxis. An example email script is uploaded to eIRB.

### 7.3 Measures

#### 7.3.1 Visit Case Report Forms

Study staff will collect key data points using eCRFs at study visits. For the baseline visit, information to be collected on eCRF includes eligibility criteria, basic demographic information, and acute HIV and STI symptoms. For follow-up visits, eCRFs will include information regarding documentation of condition crossover, number of condoms distributed and returned, adverse events, and study stops.

#### 7.3.2 Baseline Survey

The baseline questionnaire will collect self-reported demographic information, information on prior HIV testing, information on history of condom use problems, information on substance use, and information on past sexual partners. Anticipated completion time is 30-45 minutes.

#### 7.3.3 Coital Log

Participants will be instructed to complete a mobile-optimized, web-based home coital log that can be securely loaded on personal devices (e.g. smart phones, tablets, personal computers). The coital log will first ask whether the participant has had sex since their last coital log entry. If the participant has had sex, the participant will record information on whether a condom was used, partner, lubricant use, type of sex, quality of erection, clinical condom performance, and event-level sexual pleasure.

#### 7.3.4 Outcome Measures

- Pleasure, an outcome measure for Aim 1, will be measured at the event level through the coital log. Based on a literature search and consultation with experts, there is no extant event-level scale to assess pleasure. We therefore

developed and validated a measure, based on a process that included a literature review to identify relevant constructs, an external expert scientific panel consultation to develop items and identify domains, and the conduct of a survey to validate the scale through determination of internal consistency, factor analysis, and correlational (construct) validity. The validated scale resulting from this process will be the measure we use to assess pleasure.

- Preference, an outcome measure for Aim 2, will be measured at the final study visit. For each combination of crossover conditions, there will be a paired comparison asking participants to select their preferred condom between the two relevant study conditions. We will also assess preference at interim study visits prior to beginning into the third crossover condition. For analysis purposes, we will use the final study visit data for preference if available, but for participants lost to follow-up we will use interim study visit preference responses.
- Total clinical condom failure, an outcome measure for Aims 3-4, will be measured at the event level through the coital log.
    - ISO guidance defines clinical failure as combined clinical breakage and slippage.[26]
        - "Clinical breakage as a condom failure event occurring when the condom breaks during intercourse or during withdrawal from the vagina.
        - Clinical slippage is defined as a condom failure event occurring when the condom slips completely off during intercourse or during withdrawal from the vagina.
        - Slippage occurring because the user failed to hold onto the condom at the base of the penis during withdrawal and/or because of delayed withdrawal are considered user failures and should be recorded as non-clinical slippage. (These user failures should not be counted as *clinical* slippage events).
        - If a condom slips off primarily as a result of breakage, then it should not be counted as a slippage event.
        - If a condom both breaks and slips during a single used, then it is only counted as a single clinical failure."
    - As per ISO guidance specified above, condom slippage considered user error will not be considered clinical failure. Specifically, we will ask participants who experienced slippage on withdrawal whether (1) the participant held onto the base of the condom during withdrawal and (2) their penis was still hard when they pulled out of their partner's vagina/anus. Affirmative response to either of these questions will lead to the determination of user error and will not be considered to be clinical condom failure. For condom failure in which breakage and slippage occur, we will only count this as a single failure for calculation of total clinical failure rate.

### 7.4 Training

All study recruiters will complete a two-hour training on recruitment procedures and use of study screening instruments.

All study staff, including recruiters, counselors, phlebotomists, and others involved with research events will complete CITI training regarding biomedical and social/behavioral ethics in study operations and data management and good clinical practice. All study staff involved in the handling of biological specimens will be trained in Biohazard Safety (Emory University Environmental Health and Safety Office courses Research Laboratory Safety, Biosafety, and Bloodborne Pathogens for Research). All study staff who will be conducting HIV testing or phlebotomy will have certification of Hepatitis B immunization and titer. Study staff who have contact with blinded participants will be trained in how to interact with blinded participants.

All study staff who conduct HIV counseling and testing will complete a three-day training in HIV prevention counseling and rapid testing, according to the CDC training curriculum. All HIV counselors and testers will complete at least 40 hours of supervised HIV counseling and testing experience prior to independent counseling.

Those performing phlebotomy will have training in phlebotomy and will have at least 40 hours of experience drawing blood as a phlebotomist or registered nurse.

## 8. SAFETY MONITORING AND ADVERSE EVENT REPORTING

### 8.0 Safety Monitoring

To minimize risks and ensure the safety of subjects, at study visits study staff will refer to participants by their initials, not their names and keep all participant materials locked in a secure location. All electronic data will be stored in a secure environment hosted by Dacima, and copies of the dataset will be downloaded to a securely segregated SQL table on the secure (Health Insurance Portability and Accountability Act (HIPAA) Compliant) server at the Emory University Rollins School of Public Health. Any hard copy data will be secured in a locked office and locked filing cabinet.

The principal investigator has developed a data and safety monitoring plan (uploaded to eIRB). The principal investigator will monitor data collection throughout the study, and will ensure that interview protocols are followed, all adverse event reports are reviewed (if any), confidentiality procedures are implemented, and the Emory University IRB is alerted if unexpected concerns arise.

The project team will meet regularly to discuss progress toward data collection goals. At these meetings, study staff will prepare weekly reports on data collection and any emerging issues or potential problems regarding the data collection efforts. The following will be reported by the principal investigator in writing to the Emory University IRB: all serious adverse events associated with the study procedures and/or any incidents or problems involving the conduct of the study staff or subject participation, including problems with the consent processes.

## 8.1 Adverse Event Definitions and Reporting Requirements

### 8.1.1 Adverse Events Definitions

#### *8.1.1.1 Adverse Events*

An AE is defined as any unfavorable or unintended sign (including laboratory findings), symptom or disease that occurs to a subject while enrolled in a clinical trial that could be associated with the use of the study intervention. Medical conditions that exist at study enrollment are not considered an AE unless condition worsens after use of the study intervention.

In this study, the study intervention includes provision of condoms, lubricant, and HIV testing and counseling. Possible adverse events for all participants include symptomatic STI infection, acute HIV infection, discomfort or other issues related to the study condoms, and pregnancy (for current partner of MSW).

#### *8.1.1.2 Serious Adverse Events*

We do not anticipate serious adverse events occurring in this study due to the nature of the study intervention.

### 8.1.2 Adverse Events Reporting

Study participants will receive instructions to report any untoward medical occurrences that could be associated with the study intervention to study staff, except for possible life-threatening events, where they will seek immediate emergency care. If the participant receives care from a provider outside of the study for an AE, with permission of the participant, records from that visit related to the untoward medical occurrence will be received by study staff as determined by the study physician. Study staff will document all AEs observed in or reported by participants in the AE eCRF, regardless of severity of presumed relationship to the study interventions or product. Participants who experience reactions or side effects to the study condoms or lubricant may be asked to have a picture taken of the reaction. This picture will be shared only with the study clinician for AE determination and will not be entered as study data. The principal investigator will have final determination in severity, relatedness (to study intervention), and whether the AE is considered to be anticipated or unanticipated.

# 9. STATISTICAL CONSIDERATIONS

## 9.0 Study Aims

The primary aims are:

1. To compare fitted condoms with standard condoms regarding levels of reported pleasure as determined by rating per condom use event.
2. To compare fitted condoms with standard condoms regarding preference as determined by ranking of the two conditions at the study conclusion.

3. To assess for fitted, thin, and standard condoms the total clinical failure rate of each type of condom for anal sex among MSM relative to a cut-point to be determined by the FDA.
4. To compare fitted condoms with standard condoms regarding total clinical failure for anal sex.

Secondary aims:

1. To compare thin condoms with standard condoms regarding levels of reported pleasure as determined by rating per condom use event.
2. To compare fitted condoms with thin condoms regarding levels of reported pleasure as determined by rating per condom use event.
3. To compare thin condoms with standard condoms regarding preference as determined by ranking of the two conditions at the study conclusion.
4. To compare fitted condoms with thin condoms regarding preference as determined by ranking of the two conditions at the study conclusion.

Other areas of research interest:

1. To assess differences in total clinical failure between fitted, thin, and standard condoms.
2. To analyze aims regarding pleasure/preference and fitted condoms (Aims 1 and 2) restricted to participants who received fitted study condoms outside standard sizes of width, length, and both width and length.
3. To analyze aims regarding pleasure/preference (Aims 1 and 2) restricted to participants in the top and bottom deciles of self-reported penis size.
4. To explore correlates of condom failure (type of condom, SES, level of condom experience, partner genital piercings).
5. To compare history of experiencing condom slippage and breakage with slippage and breakage experienced in the study period.
6. To perform visual analysis of condom breaks, and correlates of breakage types.
7. To compare a baseline measure of perceptions of pleasure during condom use to event-level pleasure reported in the coital logs.
8. To compare previous measures of pleasure (history of pleasure using condoms) to pleasure prospectively reported during the study.
9. To assess whether there were differential changes in pleasure for certain individuals: those with history of erectile dysfunction or sexual performance issues; participants with certain penile dimensions; MSM vs. MSW.
10. To understand the clinical failure rate when a single condom is used for multiple types of sex (oral, anal, and/or vaginal), and correlates of this type of condom usage.
11. To compare history of erectile dysfunction and sexual performance issues to consistency of condom use.
12. To compare measures of pleasure between MSM and MSW enrolled in the study.
13. To understand willingness and acceptability to use condoms, and reasons why participants do not use condoms through a comparison willingness at baseline to willingness at the end of the study period.

14. To understand the stability of condom preferences over time (prior to beginning the third crossover condition and at the end of the study).
15. To assess effect modification of study arm (i.e., MSM vs. MSW) on the relationship between study condition and outcome measure (i.e., pleasure or preference) for Aims 1 and 2.

### 9.1 Study Hypotheses

Hypotheses of the primary aims are:

1. Fitted condoms will have higher pleasure ratings than standard condoms.
2. More participants will prefer fitted condoms than standard condoms.
3. All condom conditions will have clinical failure point estimates less than a cut-point level of acceptable clinical failure, with the cut-point to be determined by the United States Food and Drug Administration (FDA).
4. Fitted condoms will have a lower total clinical failure rate than standard condoms for anal

### 9.2 Study Rationale

Rationale for the primary aims are:

1. There is biological plausibility and published data indicating that condoms fitted to penile dimensions could improve perceptions of pleasure.
2. There is biological plausibility and published data indicating that condoms fitted to penile dimensions could improve perceptions of pleasure.
3. Condoms are currently recommended for anal sex use for the prevention of STI and HIV by the U.S. Centers for Disease Control and Prevention (CDC), the United Nations, and the World Health Organization.
4. Published data from a prospective, event-level assessment of clinical failure indicate that fitted condoms may have superior clinical performance for anal sex.[16]

### 9.3 Sample Size

We will seek to have at least 404 participants complete the trial. To accomplish this goal, we will target enrollment of 504 participants, estimating 20% loss to follow-up. If the loss to follow-up is greater than 20%, we may seek additional recruitment. The study will have a MSM arm and a MSW arm, with 252 participants enrolled in each arm.

Participants will be randomized into one of six possible crossover condition combinations (See Table 1). Each arm's crossover condition combination will have approximately 42 participants (See Figure 2).

### 9.4 Data Analysis

**Table 2. Outcome measures used to assess each study aim**

| | Aim | Outcome measure |
|---|---|---|
| 1 | To compare fitted condoms with standard condoms regarding levels of reported pleasure as determined | Pleasure-scale score (response item mean) for fitted condoms and standard condoms, following each coital event |

| | | |
|---|---|---|
| | by rating per condom use event | |
| 2 | To compare fitted condoms with standard condoms regarding preference as determined by ranking of the two conditions at the study conclusion | Binary preference of fitted versus standard condoms, at final study visit |
| 3 | To assess for fitted, thin, and standard condoms the total clinical failure rate of each type of condom for anal sex among MSM relative to a cut-point to be determined by the FDA | Binary occurrence of clinical failure for each type of condom, at each coital event |
| 4 | To compare fitted condoms with standard condoms regarding total clinical failure for anal sex | Binary occurrence of clinical failure for fitted and standard condoms, at each coital event |

### 9.5 Study blinding

The study statistician and the principal investigator, who are responsible for analyses and reporting results to FDA, will be blinded until after the initial analysis of study results has been lodged with FDA. Participants will also be blinded in order to minimize bias. The different condom types were matched to three different colors. These colors will be used to guide the process of condom distribution in the study. The colors, rather than the fitted, thin, and standard condom types, were entered into Dacima. Study staff who are not involved in the assessment of outcomes or analyses may be unblinded as needed to dispense the appropriate condoms to participants, but will be trained in how to interact with blinded participants.

## 10. HUMAN SUBJECTS CONSIDERATIONS

### 10.0 Ethical Review

Prior to study initiation, approval of the protocol, study documents, and informed consent process will be provided by the Emory University IRB.

### 10.1 Informed Consent

The principles of Informed Consent, according to FDA Regulations and International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), will be followed. The principal investigator will submit a copy of the proposed ICFs, together with the study protocol, to the Emory University IRB for approval.

For potential participants in the study, consent to screen will be obtained either online or verbally (over the phone) prior to conducting eligibility screening on the phone. Informed consent will be written and will be obtained at the baseline visit before any study procedures are initiated. Potential participants will be given a copy of the ICF, and a study staff member will review the form with the participant and answer any questions the participant may have. The ICF will include information on the purpose of the study, study activities and

procedures, and protection of privacy. Potential participants will be reminded that their participation is voluntary, and if they agree to participate they can withdraw from participation at any time. Participants' signing of the ICF will be witnessed by a member of the study staff, who will also sign the form. Participants will be given a copy of the signed consent form. All participants attending a baseline visit will complete the ICF prior to enrollment.

### 10.2 Risks to participants

Following are anticipated risks to participation, and procedures to reduce risk:

- **Persons may learn they have HIV or possibly an STI, and this may be upsetting.**

  To minimize this risk, we will have counselors and other study staff who have been trained in HIV counseling and testing conducting HIV testing and providing referrals to participants. Referrals for HIV treatment and care and STI testing and treatment will be made to providers familiar with MSM-specific health issues.

- **Persons may be uncomfortable with some survey questions.**

  To minimize this risk, we will be very clear during the consent process regarding the types of data that we will collect, and we will make optional questions not pertinent to key study outcomes. Participants who find the surveys to be generally uncomfortable can choose to discontinue participation in the study.

- **Persons may have their study information compromised.**

  Procedures for data security are described in section 10.6. All study staff will sign a confidentiality agreement (uploaded to eIRB).

- **Persons who have blood drawn for confirmatory HIV testing may have discomfort, bruising, or a local infection at the site of venipuncture.**

  This is a typical risk of having blood drawn in any setting. The study phlebotomists will be certified and experienced in phlebotomy, as described in section 7.4, to minimize this risk.

- **Persons using study condoms may experience condom failure.**

  Condom failure is a risk in any condom clinical trial. However, the condoms in this trial have all been cleared by the FDA. To minimize risk of condom failure, participants will be instructed in proper condom use and asked to report any issues with study condoms.

- **Persons using study condoms and lubricant may experience reactions or side effects.**

  Reactions and side effects are a risk with any condom or lubricant use. Participants with known allergies to latex or water-based lubricant will be excluded from the study. Participants with reactions or side effects to study products may be study stopped.

### 10.3 Anticipated benefits to research participants

We do not anticipate benefits to individuals, except for learning one's HIV status and receiving appropriate counseling, and being linked to treatment and care as needed. The broader community may benefit in the future, as this study is designed to allow scientists to learn more about the performance of fitted, thin, and standard condoms. The study results may be used to help others in the future by providing evidence to regulators.

### 10.4 Incentives

Participants will be reimbursed for their time and effort in this study. Participants who attend a baseline enrollment visit will be compensated $50 for the visit regardless of their eligibility or future study participation. Participants will be reimbursed $35-$50 for each follow-up visit they attend. Reimbursement will depend on completion of coital logs. Participants who complete a minimum number of coital logs in the two-week period will be compensated $50 at their follow-up visit. Participants who do not complete the minimum number of coital log entries will be compensated $35 at their follow-up visit. Compensation will be given on a reloadable ClinCard MasterCard.

### 10.5 Notifying Participants of Study Findings

We will inform participants of the results of their biomedical tests, consisting of a rapid HIV test at their baseline visit and, as needed, results of tests performed to detect acute HIV infection.

### 10.6 Participant Privacy and Confidentiality

Our efforts to protect privacy and confidentiality are evident in several areas: study procedures, training, and data management practices.

*Study Procedures:* We will collect multiple means of contact for participants during the initial study visit. For each means of contact, we will ask whether it is acceptable to leave a generic message about participation in a health study at that email address or phone number. Standardized scripts for phone and email contact will be used. Participants will be instructed to delete all study-related text messages and e-mails received and sent related to the study immediately after receiving or sending.

*Training:* All study staff will have a one-hour training on participant privacy and confidentiality. Study staff will sign a confidentiality agreement before having access to any confidential data. The confidentiality agreement will be resigned every year that the staff member is involved with the study.

*Data management practices:* Personally identifying information will be stored in a secure dataset on Dacima servers. All electronic study data will be entered directly into Dacima's secure web-based Clinical Data Management System (CDMS). Access to participant identifying information will be restricted and role-based, so that study staff who are solely responsible for scheduling can view contact information and next study visit due date, but no other study data. Similarly, study staff solely responsible for visit procedures will only be able to see the study data and the (non-identifying) study ID.

All participant documentation, data and other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the participant except as necessary for monitoring by the Emory University IRB, FDA, National Institutes of Health (NIH), and Office of Human Research Protections (OHRP).

### 10.7 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

### 10.8 Study Discontinuation

This study may be discontinued at any time by the Emory University IRB as part of its duties to ensure that research subjects are protected.

## 11. LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

### 11.0 HIV Testing

At enrollment events, an FDA-approved HIV rapid test, the INSTI HIV-1 antibody test, (PMA number: BP090032/0) will be used for HIV screening. Participants with a preliminary positive test result will receive standard counseling messages per CDC recommendations. All preliminary positive results will be confirmed with a 4th generation immunoassay with reflex by a study laboratory per CDC recommendations.[24] The results of the confirmatory testing will be returned to participants by study staff experienced in HIV care linkage. The Georgia State Health Department will be notified of confirmed HIV-positive results in accordance with the law, a procedure that will be explained to participants at consent.

### 11.1 Acute HIV Testing

At enrollment and follow-up visits, we will assess plasma viral load for participants who present with symptoms that may be indicative of acute HIV infection. We will use the Abbott RealTime HIV-1 Assay, an in vitro reverse transcription-polymerase chain reaction (RT-PCR) assay, for viral load measurements on the automated m2000 System from plasma (range of detection: 40 to 10,000,000 copies/mL).

### 11.2 Laboratory Specimens

Participants with preliminary positive HIV rapid test results will have blood drawn to be sent to the study laboratory for confirmation. Participants who are symptomatic for acute HIV infection will have blood drawn to be sent to the study laboratory for viral load testing. The study staff will adhere to standards of good clinical laboratory practice, and local standard operating procedures for specimen management including proper collection, processing, labeling, transport, and storage of specimens to the lab.

#### 11.2.1 Study laboratories will include:

1. Quest Diagnostics

2801 N Decatur Rd Suite 185
Decatur, Georgia 30033-5924

2. Kraft Labs
   101 Woodruff Circle, Room 7007
   Atlanta, Georgia 30322

### 11.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all study staff in the drawing of blood, as currently recommended by Occupational Safety and Health Administration (OSHA).

## 12. ADMINISTRATIVE PROCEDURES

### 12.0 Data Collection, Entry and Management

Study data collection will be predominantly electronic, and based on the Dacima CDMS platform. Dacima CDMS is a secure data collection tool that allows users to create online data collection forms, instruments, and databases, and can be implemented to allow compliance with FDA standards, specifically Title 21 CFR Part 11. For all office visits, eCRFs and electronic surveys will be conducted. Because Dacima uses a web-based application, participants will receive a link to be able to complete electronic coital logs at home with a range of devices that have web browsers, including smart phones, tablets, and personal computers. We will provide smartphones for participants who do not have access to web browsers at home so they are able to complete the coital logs immediately after each study condom use.

Information collected during recruitment and phone screenings will not be collected using Dacima's system, but instead will be collected through surveygizmo, and transferred into a secure Emory database that allows for potential participants to be contacted regarding the study. Surveygizmo has a HIPAA BAA with Emory University that will apply to data collected in the course of the screening process. None of the data collected during recruitment and phone screenings will be used as part of the study dataset.

At the enrollment visit, study staff will review a sample home coital log with each participant to familiarize them with this means of data collection. Additionally, self-reported data entry into the Dacima system during the baseline visits will allow participants to gain experience in electronic survey completion in the Dacima format, facilitating the ability to complete forms at home in real time following sexual acts.

Study staff will require participants to create a unique username and password at enrollment. For coital log entries, participants will use a secure link to access study forms that require username and password to login.

### 12.1 Quality Assurance

Monitoring visits will be made periodically by the principal investigator during the study to ensure that all aspects of the current, approved protocol/amendment(s) are followed. The study may also be subject to a quality assurance audit by the sponsor or its designees, as well as inspection by appropriate regulatory authorities.

All eCRFs and electronic surveys will be programmed into Dacima and will include skip patterns to ensure that participant and staff responses to each question are logical based on responses to previous questions. Data entry fields will include data validation and range limits, when appropriate, to ensure responses are reasonable. Study staff entering data can create and save queries in Dacima on data forms to double check responses and source documents. Coital logs will be reviewed by study staff with the participant at each follow-up visit to ensure accuracy and completion.

### 12.2 Regulatory Requirements

The study will be conducted in accordance with Title 21 CFR Part 11 and GCP guidelines. The study will obtain Emory University IRB approval for the protocol and Informed Consent forms prior to initiating the study. All changes to the protocol will be submitted to the Emory University IRB for review and approval as appropriate.

### 12.3 Institutional Review Board

Prior to initiating the study, the principal investigator will submit the following to the Emory University IRB: the verbal and electronic consent for screening, informed consent, this protocol, and materials used to recruit subjects for this clinical trial. No subjects will be recruited until documented IRB approval is obtained. Any addendums to the above documents will be resubmitted to the Emory University IRB for review and approval. The principal investigator will follow the requirements of Emory University's IRB on periodic reporting of the progress of the study, reporting of serious or unexpected adverse events, and safety monitoring reports.

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