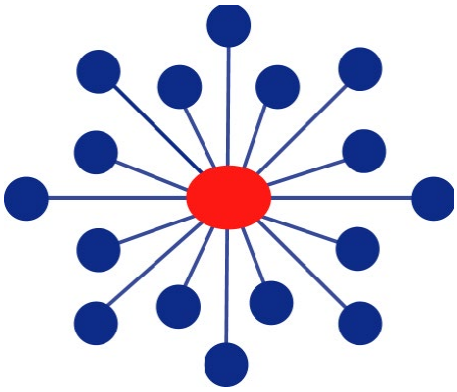

NIDA CTN Protocol 0083

Using Social Media to Deliver HIV Self-Testing Kits and Link to Online PrEP Services (Social Media PrEP)

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Funded by: National Institute on Drug Abuse (NIDA)

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CONFIDENTIALITY STATEMENT

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1.0 LIST OF ABBREVIATIONS

AE	Adverse Event
AHF	AIDS Healthcare Foundation
AIDS	Acquired Immunodeficiency Syndrome
CAPA	Corrective and Preventative Action
CCC	Clinical Coordinating Center
CCTN	Center for the Clinical Trials Network
CDC	Centers for Disease Control and Prevention
CoC	Certificate of Confidentiality
CRF	Case Report Form
CTN	Clinical Trials Network
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
eICF	Electronic Informed Consent Form
ETR	Education, Training and Research
FDA	Food and Drug Administration
GBMMS	Group-Based Medical Mistrust Scale
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HOPE	Harnessing Online Peer Education
IRB	Institutional Review Board
LN	Lead Node
MOP	Manual of Operating Procedures
MSM	Men who have sex with men
NIH	National Institutes of Health
NIDA	National Institute on Drug Abuse
OHRP	Office for Human Research Protections
PI	Principal Investigator
PRB	Protocol Review Board
PrEP	Pre-Exposure Prophylaxis
QA	Quality Assurance
RHBA	Rapid HIV Behavioral Assessment
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SOP	Standard Operating Procedure
SSO	Single Sign On
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
TAPS	Tobacco, Alcohol, Prescription medication, and other Substance use
TTM	Transtheoretical Model
TDF–FTC	Emtricitabine - tenofovir disoproxil fumarate
UCLA	University of California, Los Angeles
WHO	World Health Organization
YTH	Youth Technology and Health

2.0 STUDY SYNOPSIS

2.1 Study Objectives

The **primary objective** of this study is to compare the relative effectiveness of three web-based platforms: social media sites (e.g., Facebook), dating applications [apps] (e.g., Grindr/alternative), and informational sites (e.g., Google) to promote self-testing of Human Immunodeficiency Virus (HIV) infection among men who have sex with men (MSM) who are at increased risk of HIV exposure and/ or infection. In addition, we will measure Pre-Exposure Prophylaxis (PrEP) uptake and evaluate the degree to which substance use and, separately, the participant's intention to test affect HIV self-testing and PrEP uptake. Through this research, we will also examine how participants' social media use, attitudes on HIV testing, perceptions of sexual risk behavior, medical mistrust, and stigma impact HIV testing and PrEP uptake.

2.2 Study Design and Outcomes

This will be a longitudinal study recruiting users from social media sites (e.g., Facebook), dating applications (e.g., Grindr/alternative) and informational sites (e.g., Google) who order HIV home self-test kits through advertisements developed by the study team.

There is one **primary outcome** of this study:

The primary outcome is the number of HIV home self-test kits ordered per day (i.e., number of study participants ordering an HIV home self-test kit per day) by promotional platform (social media, informational, dating sites). Without loss of generalizability, the primary outcome can also be defined as the number of HIV home self-test kits ordered per a given period since this is simply a transformation. For example, one could calculate number of kits ordered per 30 days, per 100 days, etc. The number and timing of HIV self-testing kit orders will be recorded and analyzed to evaluate the effectiveness of the sites in promoting HIV self-testing. We assume that it will be rare for participants to order multiple copies of kits. If this occurs, we will analyze only the first occurrence.

Secondary outcomes will include:

1. The number of participants who used the study-provided HIV home self-test kit by 60- day follow-up.
2. The number of participants who tested positive for HIV using the study-provided home test kit by 60-day follow-up.
3. The number of participants who reported a high-risk substance abuse profile at baseline who ordered an HIV home self-test kit.
4. The number of participants who reported a high-risk substance abuse profile at baseline who reported seeking PrEP services or started PrEP at either follow-up.
5. The number of participants in the "Determination" stage of change at baseline who ordered an HIV home self-test kit.
6. The number of participants in the "Determination" stage of change at baseline who reported seeking PrEP services or started PrEP at either follow-up.
7. The number of participants who tested positive for HIV using the study-provided home test kit and were linked to care within 30 days after the self-reported test date.
8. The number of participants who tested positive for HIV using the study-provided home test kit,

were linked to care and started treatment within 30 days after self-testing.

9. The number of participants who tested negative for HIV using the study-provided home test kit and sought PrEP services within 30 days after self-testing.
10. The number of participants who tested negative for HIV using the study-provided home test kit, sought PrEP services and started PrEP within 30 days after self-testing.
11. The amount of money spent per test kit ordered per promotion type, including all the costs of the intervention (advertisement, test kit).
12. The proportion of people from each website and the proportion of people from each type of website who clicked on advertisements.
13. Kit ordering rates expressed as kits ordered per unique participants visiting the study informational page on Qualtrics.
14. The number of participants with high rate of sexual delay discounting at baseline who ordered an HIV home self-test kit.

A detailed description of the above-mentioned primary and secondary outcomes can be found at Section 7.0.

2.3 Sample Size and Study Population

The study will enroll approximately 400 MSM (or an appropriate number of participants until approximately 400 test kits have been ordered) aged 18-30 years, inclusive, who are at increased risk of HIV exposure and/or infection and who use social media sites, dating apps, and/or informational sites. Based on the inclusion criteria, it is anticipated that participants will be male, specifically Latino and/or Black/African American, who report high-risk sexual behavior with men (condomless anal sex, multiple partners of unknown HIV status), not currently on PrEP or have not taken PrEP in the past 6 months and have not tested for HIV in at least the past 3 months. We aim to recruit MSM who self-identify as Latino and/or Black/African American due to the increased risk for HIV exposure and undiagnosed infection in these minority populations.

2.4 Assessment and Duration

This is an observational, non-randomized cohort study that will assess participants at three timepoints over the course of two months. The study will recruit approximately 400 participants using advertisements posted on online sites, categorized into three groups: social media, dating, and informational sites. It is anticipated that enrollment may take approximately 9 months, with data collection anticipated for completion approximately 11 months after the start of enrollment.

We will compare the results of targeted HIV self-testing advertisements placed on the three web platform categories. Identical campaigns with similar targeting strategies will promote HIV testing and PrEP uptake on 9 sites (Facebook, Instagram, Twitter [social media sites], Grindr/alternative, Jack'd, and Hornet [dating apps], and Google, Bing, and Yahoo [informational sites]). After clicking the ad, participants will be brought to the study informational page on Qualtrics. Participants interested in study participation will provide online informed consent. Those enrolled will be asked to fill out a baseline survey and then instructed to visit a webpage where they can securely request a free mailed HIV home test kit, PrEP educational materials and referral information for HIV care or PrEP depending on HIV self-test results. Participants will be asked to complete follow-up assessments at 14-days and 60-days post-baseline. Participants will be compensated for their time via electronic gift cards upon completion of each assessment.

Each participant will be part of the study for approximately 2 months. Baseline evaluations and follow-

up will each require approximately 20 minutes to complete. Upon completion of the follow- up, three months will be required for data analysis.

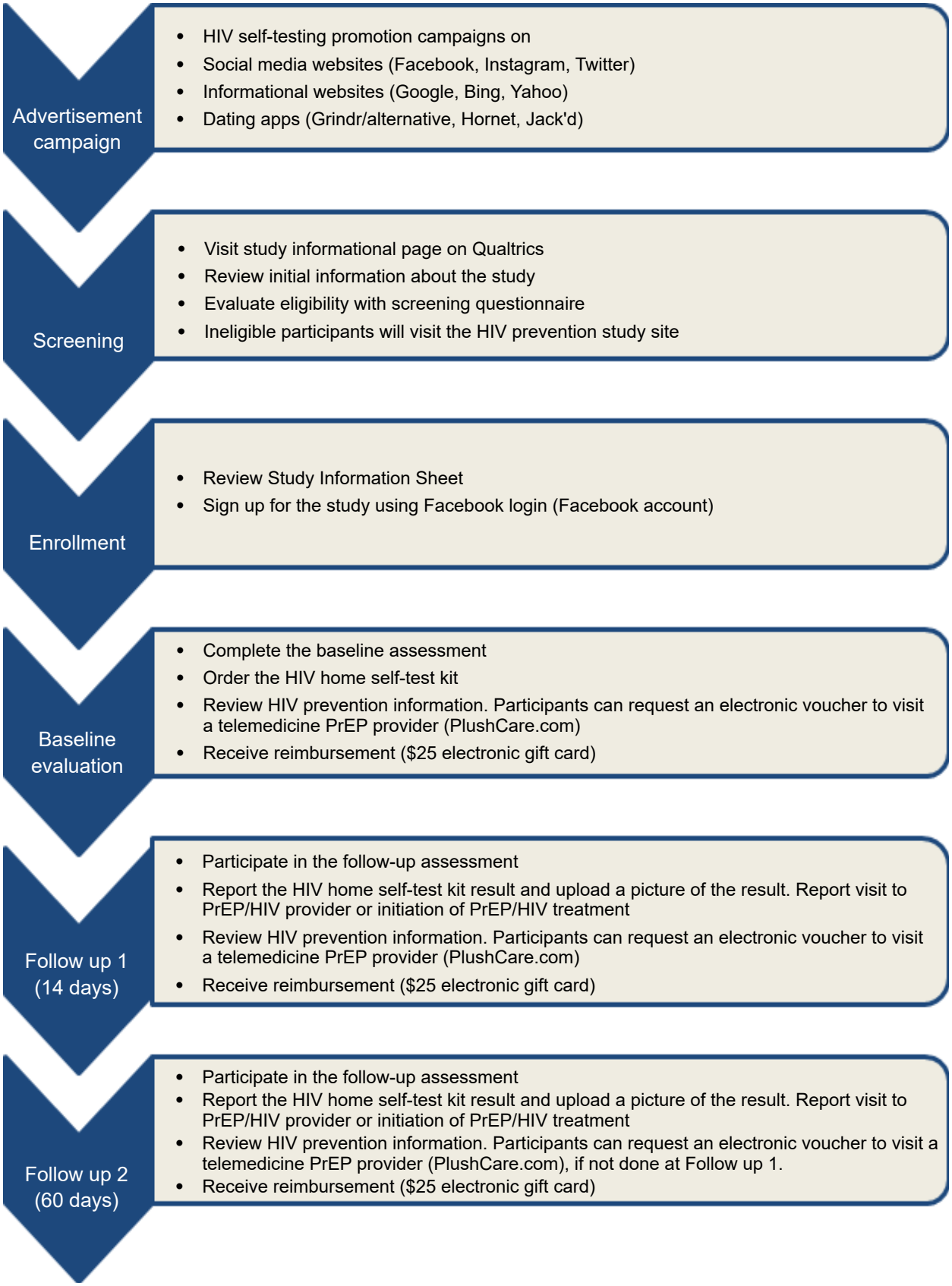
2.5 Safety Reporting

This is a minimal risk study, thus Adverse Events (AEs) and Serious Adverse Events (SAEs) are expected to rarely occur. Any AEs and SAEs reported/collected in accordance with the protocol will be reported to the University of California, Los Angeles (UCLA) Institutional Review Board (IRB) following that institution's policies and procedures. Additionally, a list of any study-specific self-reported AEs/ SAEs will be provided to the Lead Node (LN) Regulatory Coordinator upon request or at any scheduled monitoring visit and to the Protocol Review Board on an at-least annual basis.

2.6 Analyses

The primary outcome is the number of HIV home self-test kits ordered per day (i.e., number of study participants ordering an HIV home self-test kit per day) by promotional platform (social media, informational, dating sites). Without loss of generalizability, the primary outcome can also be defined as the number of HIV home self-test kits ordered per a given period since this is simply a transformation. For example, one could calculate the number of kits ordered per 30 days, per 100 days, etc. The number and timing of HIV self-testing kit orders will be recorded and analyzed to evaluate the effectiveness of the sites in promoting HIV self-testing. We assume that it will be rare for participants to order multiple copies of kits. If this occurs, we will analyze only the first occurrence. The analysis model will be a Poisson regression model that will use time as an offset. Secondary and exploratory analyses will be conducted using univariate tests and descriptive statistics such as counts, percentages, and 95% confidence intervals.

3.0 STUDY SCHEMA



3.1 Key Research Site Roles

UCLA: Study overview, Recruitment, Participant follow-up, Data collection and data management, regulatory management
Site Role (Minimum Degree Requirement)
Site Principal Investigator (MD or PhD)
Research Coordinator (Master's degree or bachelor's plus equivalent experience)
Research Assistant (Bachelor's degree)
Dartmouth College: Data analysis, regulatory coordination, study overview
Site Role (Degree Requirement)
Site Principal Investigator (MD or PhD)
Research Coordinator (Master's degree or bachelor's plus equivalent experience)

4.0 INTRODUCTION

4.1 Background and Significance to the Field

Despite accounting for a small fraction of the U.S. population (6%), men who have sex with men (MSM) account for a majority of those infected with HIV and experience the largest burden of new infections[1]. Those 18-30 years of age account for approximately two-thirds of all new HIV infections, and a vast majority of these infections result from male-to-male sexual contact[2]. Nearly half of those individuals do not know that they are infected[2]. It is essential that prevention efforts directly focus on MSM as a targeted high-risk group to prevent new infections by facilitating HIV testing and Pre-Exposure Prophylaxis (PrEP) uptake.

HIV testing and use of PrEP medication are two of the most promising methods for reducing HIV transmission rates. HIV testing leading to treatment can reduce the transmission of infection by 95%[3]. Aside from the 'traditional' point-of-care laboratory or rapid tests, the World Health Organization (WHO) has endorsed the use of self-testing to increase awareness of HIV infection status[4]. The OraQuick® Home HIV test kit [OraSure Technologies, Inc., PA] is an FDA-approved self-test kit that detects HIV antibodies in oral fluid. The kit is commercially available in pharmacies and online, and it has been proven to be acceptable and user-friendly. The research team has utilized this kit in previous screening programs[5-6].

Transmission rates can further be reduced with PrEP. PrEP is the combination of two antiviral drugs (tenofovir–emtricitabine; TDF–FTC) in the form of a daily pill that prevents new infections. Randomized controlled trials in high-risk populations have shown that infection rates with PrEP use drop dramatically, as low as 0%[7]. The Centers for Disease Control and Prevention (CDC) recommends prescribing PrEP to all adults with substantial risk for HIV infection[8]. Nevertheless, PrEP awareness[9] and most importantly uptake has been slow, especially among young (ages 18- 24) Black-and-Latino MSM[10-11].

Substance use is prevalent among young MSM[58] and is associated with condomless anal sex, a key risk factor for new HIV infection[59]. Further, Patel et al.[16] reported that some young Black and Latino MSM used social media to exchange sex for money or drugs, behavior that increases risk of HIV transmission. Substance use is also associated with this high-risk population's likelihood of HIV testing and PrEP uptake. Among young, Black MSM, binge drinking is associated with decreased odds of recent HIV testing [60], while heavy marijuana use is associated with increased likelihood of unknown HIV infection[61]. Substance use is prevalent among MSM users of social media. In a study among 118 Latino and Black MSM Facebook users, we reported high prevalence of marijuana, methamphetamine and cocaine use[15]. Among internet-using MSM, only 85% had ever tested for HIV and only 58% had tested in the last year, and both younger age and substance use are associated with lower likelihood of testing, indicating an unmet need for HIV testing promotion among these subpopulations[62].

The exponential popularity of social networking sites has drawn scholarly attention in recent years, and rapidly growing efforts have been made in applying these websites to behavioral health interventions. Nearly 7 out of 10 Americans use social media to connect with one another, engage with news content, share information and entertain themselves[12]. Compared to all other age groups, regardless of sexual preferences, those between 18-30 years are the age group that is most likely to be active and engaged in daily social media use[13]. Facebook is the most popular social media platform among other platforms, including Instagram and Twitter. Social media is also a new way to meet sex partners. Young MSM frequently use social media, including dating- centered applications ("apps") like Grindr, to connect with new sex partners[13]. In a recent study by Goedel et. al.[14] among 92 young gay and bi-sexual men, participants reported that they used Grindr to find sexual partners, had accounts in multiple other

dating apps, and spent nearly one hour a day using these apps.

To our knowledge, it is not yet known whether leveraging social media sites or dating apps—the current online methods for recruiting and engaging HIV participants—is the more effective method for health promotion among participants at risk for HIV and related substance use. Because users may be in a more action-oriented stage of change when seeking HIV information on informational sites such as Google, they might be more ready to engage in health services. It is possible that these individuals could be more likely to click on an HIV self-testing-focused ad as well as actually seek testing and PrEP services. Although substance use is associated with lower rates of HIV testing among MSM, how substance use impacts likelihood of HIV home self-testing when MSM are recruited online is underexplored. This study seeks to address these questions.

Significance to the Field

HIV infection results in a substantial personal, societal, and financial cost at a global scale. HIV infection is a preventable public health issue that can be addressed by harnessing the established infrastructure and outreach of massive social media and informational services. Those platforms may be utilized to deliver empirically-established prevention interventions, such as HIV self- testing, PrEP or viral load suppression, in a cost-effective way to thousands of users. Furthermore, those platforms allow for a distribution approach that is not tied to a specific geographic region, allowing for future fully-automated and nation-wide or global HIV prevention campaigns. Additionally, this study aims to identify which types of social media or online platforms are the best tools to use for reaching a specific population and inform targeted/focused approaches to reach MSM, including those who may be at increased risk due to substance use.

Study Rationale

This study seeks to evaluate the effectiveness of an online campaign promoting HIV self-testing on different web platforms: social media sites (Facebook, Instagram, Twitter); dating apps (Grindr/alternative, Hornet, Jack'd); and informational sites (Google, Bing, Yahoo). The primary objective of this study is to compare HIV self-testing uptake among users of the three different online platforms. Secondary aims will seek to evaluate differences in PrEP uptake, as well as the impact of key moderator variables—substance abuse and stage of change—on HIV testing and PrEP uptake. Other secondary and exploratory aims will seek to evaluate the impact of perceptions and attitudes on HIV testing and PrEP uptake. Please see Section 5.0 for a complete listing of all secondary objectives. Each campaign will include similar advertisements, developed by the study team as part of the project, and will be employed across all three platforms (9 sites total) with the same effort in terms of time and money spent for advertising (so these variables are held constant across conditions). Study participants will be divided into three groups based on the platform from which they were recruited. During the campaign, we will send approximately 400 coupon codes redeemable for free HIV self-test kits to eligible participants. There will not be a pre-specified number of participants per platform (social media, informational site, dating apps) or site (Facebook, Instagram, Twitter, Grindr/alternative, Hornet, Jack'd, Google, Bing, Yahoo). We will follow up with each participant at two intervals (14-days and 60-days after baseline) to collect the data necessary to evaluate the study objectives.

We hypothesize that participants' psychological state of motivation for HIV testing will be different when they are browsing social media sites compared to informational sites or dating apps. For example, when users are browsing dating apps and social media sites, they are typically intending to meet friends or romantic partners, not searching for health information. Alternatively, when using informational sites, users are typically searching for information (for example, they may be searching for places to test for HIV or access PrEP), creating an opportunity to engage MSM who are more willing to seek testing. We

expect that HIV self-test uptake will be higher among persons who use informational sites compared to persons using social media sites or dating apps.

Social media sites have been used as a platform for HIV prevention communication, including the dissemination of information, promotion of healthy behaviors and medication adherence, and to provide social support[17-21]. The use of pre-existing services like Facebook and Grindr has benefits not found in person-to-person text messaging platforms, as these websites can readily connect those at risk to peers and professionals[21]. Social media advertising platforms make it easier to reach out to MSM, without wasting resources on those to whom promotional materials do not apply. Those individuals falling into specific age groups (young adults) and of a specific sex (male) can be targeted by advertising platforms with ease. Previous studies have used social media sites for a range of HIV prevention efforts[21-22], but little is known about the relative effectiveness of each different platform. Several studies, including our own prior work, have shown a strong but complex relationship between online sex seeking behavior and substance use[23-26].

While social media sites target demographics and behavior, informational sites focus on advertising to users browsing on informational sites by integrating data from what is privately typed into search bars. MSM may privately search for HIV prevention related materials or gay entertainment or news but may not publicly post content about personal HIV prevention interests to social media sites. Targeted advertising through informational sites reaches over 90% of global internet users, serving over one trillion advertisement impressions to more than one billion users per month[27]. Although different in nature from social media sites, they represent a highly promising additional avenue for outreach.

4.2 Known Risks and Benefits from Interventions

Risks to Participants. The primary potential risks to participants due to study participation are psychological and social in nature. Participants could experience psychological distress, such as anxiety when discussing issues related to personal experiences (e.g., substance use, sexual history). However, we do not expect any serious events to occur based on our experience across multiple previous studies[5-6, 28-29]. Participants may experience some stress related to the knowledge of their HIV status; however, the likely harmful consequences of learning one's HIV status are low. Participation in this study may cause **social harm** (e.g., discrimination, rumors) if the involvement of the participant becomes known to others.

Protection against Risk. To protect against psychological harm, participants will be given information and education about the nature of HIV infection, HIV treatment and how to access counseling and treatment services in their area. The kit contains contact information to a 24/7 helpline, where trained operators are able to provide acute crisis counseling and refer participants to longer-term counseling measures as needed. The risk of loss of privacy (potentially leading to social harm) will be minimized using standardized data collection protocols, encrypted password- protected datasets, and trained staff with regular supervision, who have taken an oath of confidentiality. All study participants will be assigned a unique participant ID that does not include personally identifying information such as initials, date of birth, or Facebook login information. However, as a retention strategy for the 14- and 60-day follow ups, participants will be asked to provide a private phone number (cell or landline), as well as their email address, and, if possible, the name, cell phone and email address of at least one friend.

All identifiable contact information will only be accessible by study staff who need it in the course of their work and will be kept unlinked in a secure, encrypted, password-protected, study-specific UCLA server, and in a separate file from all participant IDs at all times, with the linking key only available to specific key staff members of the team to protect confidentiality. Only members of the study team will have access to electronic files through encrypted UCLA connections.

Participant information will be kept private using the following measures. Randomly generated participant identification numbers will be assigned to each participant's e-mail address upon providing their consent to participate in the study. The study team will assign these identification numbers to participants. The code key will be kept separate from the data, and all data will be de- identified during analysis. The biggest risk in using Facebook accounts to enroll in the study is a loss of confidentiality. Participants' enrollment is linked to their Facebook account; if they click on an ad for the study, that content can be accessed by Facebook as well as any individual hackers. While Facebook can collect information about an individual's participation in the study, they cannot do so directly. They would need to see that a participant has clicked on the study ad, then visited the study informational page. In order to maintain participant privacy, individual e-mails will be sent to each participant. Other participants will not be included or copied in these e-mails in order to protect participant privacy. While we will request an e-mail address from participants, participants will be encouraged to create a secondary e-mail account if they are uncomfortable with sharing a primary e-mail address.

Potential Benefits to Participants and Others. The potential benefits to participants include receiving information about local HIV testing, Sexually Transmitted Disease (STD) testing, and preventive services like PrEP. In addition, participants may learn about their HIV status, which, if positive, could lead them to access early treatment and services. If the participant tests HIV- negative, this may lead them to access HIV prevention services, including PrEP. Beyond the potential benefits to the participant, this study may contribute to the national goal of improving the frequency of HIV self-testing and utilization of prevention services among high-risk MSM. Early diagnosis and timely treatment of HIV are associated with better health outcomes at the individual level and reduced transmissibility at the community level. Knowledge of HIV status is not only vital for timely treatment but will become a cornerstone for the scaling up of critical biomedical services.

We estimate that the potential benefits from participating in the study and participating in the interventions outweigh any potential risks to the participants.

5.0 OBJECTIVES

5.1 Primary Objective

The main objective of this study is to compare the effectiveness of HIV self-testing promotion between three web-based platforms: social media sites (Facebook, Instagram, Twitter) versus informational sites (Google, Bing, Yahoo) versus dating apps (Grindr/alternative, Hornet, Jack'd). To accomplish this goal, the number and timing of HIV self- testing kit orders will be recorded over approximately a 30- to 45-day period and analyzed to evaluate the effectiveness of the sites in promoting HIV self-testing.

5.2 Secondary Objective(s)

1. Compare the **PrEP uptake** across social media sites versus informational sites versus dating apps. Using the study design as it is developed for the primary outcome (advertisements, screening, enrollment, and follow-ups), we will measure the number of participants who report that they visited a PrEP provider or started PrEP by the end of the study.
2. Determine how **substance use modifies HIV testing and PrEP uptake**. We will measure each participant's substance use at baseline to understand how high-risk substance use may affect the promotion of HIV self-testing (primary outcome) and the PrEP uptake (secondary outcome). We hypothesize that those with more complex substance use history and severity will be less likely to order an HIV self-test kit and less likely to uptake PrEP.
3. Determine how the participant's psychological **stage of change or readiness for HIV testing varies by recruitment method and how the stage impacts the main outcome**. We will measure each participant's stage of readiness for HIV testing at baseline to understand how this may affect the promotion of HIV self-testing (primary outcome) and PrEP uptake (secondary outcome). We hypothesize that those closer to the "action" (i.e. Determination) stage will be more likely recruited through informational sites and will be more likely to order an HIV home self-test kit and start PrEP.
4. Determine the most efficient web-based platform for advertisements related to promotion of HIV home self-test kits (primary outcome) and PrEP uptake (secondary outcome) using conversion from web-based metrics of the chosen platforms.
5. Determine how the **impact of participant perceptions about HIV testing and PrEP, stigma, and mistrust of medical providers** affects HIV home self-testing (primary outcome).
6. Determine how participants' **rates of sexual delay discounting relate to risk behavior and HIV testing.** Specifically, we hypothesize that higher rates of sexual discounting will relate to increased risk behavior and increased likelihood of HIV testing at follow-up.

6.0 STUDY DESIGN

6.1 Overview of Study Design

Culturally appropriate advertisements (designed specifically for the study population and advertisement method) for promoting HIV testing and PrEP uptake will be created by the study team. These advertisements will be placed on social media sites (Facebook, Instagram, Twitter), informational sites (Google, Bing, Yahoo) and dating apps (Grindr/alternative, Hornet, Jack'd) in the form of blast advertisements ("ads"). The advertisements will display on specific days and times (e.g., high traffic utilization) in the geographical locations selected for participation in the study.

Upon clicking the ad, users will land on the study informational page on Qualtrics, where they will receive information about the study, undergo eligibility screening and, if eligible, electronically sign the informed consent. Participants will receive information about HIV testing and PrEP and will be asked to complete the baseline assessment and order their HIV home self-test kit.

Participants will be followed up at two intervals after the baseline assessment. The first will occur **14 days post-baseline**, where participants will be asked about their test use and may be asked if they visited a PrEP provider and/or if they started PrEP and about PrEP opinions and facilitators and barriers. If they tested positive for HIV on the home self-test kit, they will be asked whether they have visited an HIV treatment provider. Participants will be asked to upload a picture of their test result for validation on the secure Qualtrics server during the 14-day follow-up assessment. Photographs will be interpreted by the study team and the result will be entered into the study database; photographs will then be deleted.

At the **60-day follow-up**, all participants will be asked to respond to study evaluation questions. Additionally, participants may respond to a subset of the questions that is the same as the 14-day follow-up, based on their responses on the first follow-up survey. Those who reported that they received a negative HIV self-test result and started PrEP at the 14-day follow-up will not be asked to answer these questions at the 60-day follow-up. Participants who either did not take the HIV test or did not start PrEP by the 14-day follow-up may be asked about PrEP facilitators and barriers, their self-test use, if they visited a PrEP provider, whether they started PrEP, and if applicable, whether they have visited an HIV treatment provider, depending on their responses during the 14-day follow-up. Participants will be asked to upload a picture of their test result (unless provided at the 14-day follow-up) for validation on the secure Qualtrics server during the 60-day follow-up assessment. Photographs will be interpreted by the study team and the result will be entered into the study database; photographs will then be deleted.

Participants who report a preliminary positive, invalid, or indeterminate result on the HIV home self-test kit will be referred to local brick-and-mortar clinics for additional services and asked to continue participating in follow-up assessments. Regardless of their result, all participants will be offered information on HIV and STD prevention, and locations of clinics and PrEP providers near them.

Data will be collected both indirectly from each website's metrics and directly from the online questionnaires that the participants will complete.

6.2 Duration of Study and Visit Schedule

Each participant will be part of the study for approximately two months. Participation in the study will begin with study enrollment (including eligibility screening, review of the study information sheet) and the completion of the baseline assessment (which in rare instances may occur over a period of days;

if so, the date of completion shall be considered the baseline date). Follow-up assessments will be scheduled via email for 14- and 60-days post-baseline.

Overall, enrollment for participants is anticipated to take approximately 9 months, with final data collection spanning up to two additional months; data lock is anticipated for approximately 12 months post-baseline.

7.0 OUTCOME MEASURES

7.1 Primary Outcome Measure

The primary outcome is the number of HIV home self-test kits ordered per day (number of study participants ordering an HIV home self-test kit per day) by promotional platform (social media, informational, dating sites). Without loss of generalizability, the primary outcome can also be defined as the number of HIV home self-test kits ordered per a given period. For example, via a transformation, one can calculate the number of kits ordered per 30 days, per 100 days, etc. The primary outcome will be measured by the number of home HIV test kits ordered through the electronic study system by promotional platform. These data will allow the study team to link individual kit orders to study participants, and to promotional platform.

7.2 Secondary Outcome Measure(s)

Secondary outcomes will be measured in the following ways:

1. The number of participants who used the study-provided HIV home self-test kit by 60-day follow-up will be collected via self-report at the time of follow-up (either 14-day or 60-day).
2. The number of participants who tested positive for HIV using the study-provided home test kit will be collected via self-report and/or sent as an image to the study team, at the time of follow-up (either 14-day or 60-day).
3. The number of participants who reported a high-risk substance abuse profile at baseline who ordered an HIV home self-test kit. Participants' substance abuse profiles will be collected via the TAPS Tool at baseline. These data will be used to characterize the sample, examine differences across platform types, and determine how substance abuse modifies the primary outcome of HIV testing.
4. The number of participants who reported a high-risk substance abuse profile at baseline who reported seeking PrEP services or started PrEP at either follow-up. Similarly, participants' substance abuse profiles will be collected via the TAPS Tool at baseline. These data will be used to characterize the sample, examine differences across platform types, and determine how substance abuse modifies the secondary outcome of PrEP uptake.
5. The number of participants in the "Determination" stage of change at baseline who ordered an HIV home self-test kit. Participants' stages of change or readiness for HIV testing will be collected via the Transtheoretical Model (Stage of Change) tool at baseline. These data will be used to characterize the sample, examine differences across platform types and determine how stage of change modifies the primary outcome of HIV testing.
6. The number of participants in the "Determination" stage of change at baseline who reported seeking PrEP services or started PrEP at either follow-up. Participants' stages of change or readiness for HIV testing will be collected via the Transtheoretical Model (Stage of Change) tool at baseline. These data will be used to characterize the sample, examine differences across platform types and determine how stage of change modifies the secondary outcome of PrEP uptake.
7. The number of participants who tested positive for HIV using the study-provided home test kit and were linked to care within 30 days after self-testing will be collected via self-report in a study-designed questionnaire at the time of follow-up (14-day or 60-day).
8. The number of participants who tested positive for HIV using the study-provided home test kit

and started treatment within 30 days after self-testing will be collected via self-report in a study-designed questionnaire at the time of follow-up (14-day or 60-day).

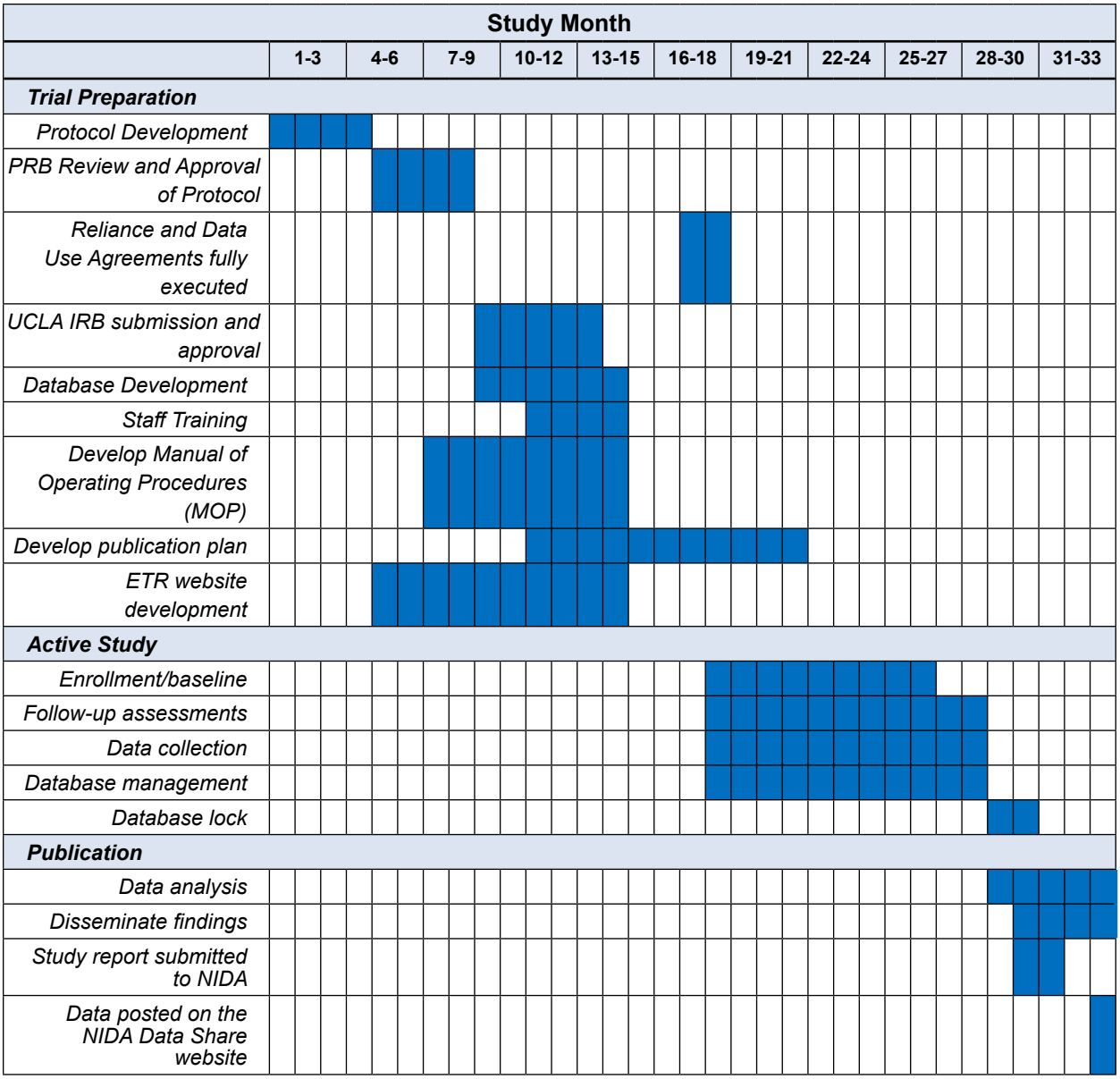
9. The number of participants who tested negative for HIV using the study-provided home test kit and sought PrEP services within 30 days after self-testing will be collected via self- report in a study-designed questionnaire at the time of follow-up (14-day or 60-day).
10. The number of participants who tested negative for HIV using the study-provided home test kit and started PrEP in 30 days after self-testing will be collected via self-report in a study-designed questionnaire at the time of follow-up (14-day or 60-day).
11. The amount of money spent per test kit ordered per platform type, including all the cost of the intervention (advertisement, test kit), will be collected via website metrics (i.e., conversion), data from the follow up (14-day or 60-day), and internal tracking of the expenses related to the implementation of the intervention.
12. The proportion of people from each website and the proportion of people from each type of website who clicked on advertisements, will be collected via website metrics from each website.
13. Kit ordering rates expressed as kits ordered per unique participants visiting the study informational page on Qualtrics. This can be calculated using the same approach as in the primary analysis, except that we will use number of visiting participants rather than time as the offset. As in the primary analysis, we assume that it will be rare for participants to order multiple copies of kits, although visits to multiple websites may be more common. If there are one or more orders within a wave, we will use only the first order, together with its website. If there are multiple websites with no orders, we will use the first website.
14. The number of participants with high rate of sexual delay discounting at baseline who ordered an HIV home self-test kit will be collected via the Sexual Discounting Task tool at baseline. These data will be used to characterize the sample, examine differences across platform types, and in moderator analyses to determine how substance abuse modifies the primary outcome of HIV testing and secondary outcome of PrEP uptake.

7.3 Study Timeline

After receiving Protocol Review Board (PRB) approval of the protocol, trial preparation activities will span approximately 4-6 months prior to commencing enrollment. Trial preparation will include the following: obtaining IRB approval, developing the data collection systems, developing the manual of operating procedures, conducting all staff training, website and advertisement development, and planning and implementing the promotion strategy on the platforms included in the study. If feasible, the study may be implemented in a single wave; however, social media sites may launch advertisements on a rolling basis. Recruitment and enrollment are expected to take approximately 9 months, with follow-up continuing for approximately 2 months post completion of the recruitment phase. Two additional months will be allowed for data lock after the end of the follow-up period. Data lock is projected to occur at approximately 20-22 months after PRB approval of the final protocol.

Table 1: Study Timeline

Approximate Timeframe for Completion of Study Activities


Study Month
1-3
4-6
7-9
10-12
13-15
16-18
19-21
22-24
25-27
28-30
31-33
Trial Preparation
Protocol Development
PRB Review and Approval of Protocol
Reliance and Data Use Agreements fully executed
UCLA IRB submission and approval
Database Development
Staff Training
Develop Manual of Operating Procedures (MOP)
Develop publication plan
ETR website development
Active Study
Enrollment/baseline
Follow-up assessments
Data collection
Database management
Database lock
Publication
Data analysis
Disseminate findings
Study report submitted to NIDA
Data posted on the NIDA Data Share website

8.0 STUDY POPULATION

The study will recruit approximately 400 MSM who actively use social media sites, dating apps, and informational sites.

8.1 Participant Inclusion Criteria

Individuals must meet all of the inclusion criteria in order to be eligible to participate in the study. Individuals participating in the study must:

1. Have clicked on one of the study-specific advertisements posted on the platforms/ websites described in this protocol;
2. Have been biologically born male (cis-gender man), per participant self-report;
3. Report condomless anal intercourse and more than one male sex partner in the 90 days prior to the date of the screening questionnaire;
4. Be between the ages of 18-30 years old, inclusive;
5. Self-identify as Latino and/or Black/African American;
6. Not currently on PrEP and haven't taken PrEP in the last six months prior to the date of the screening questionnaire (per participant self-report);
7. Have not tested for HIV in the last 3 months prior to the date of the screening questionnaire (per participant self-report);
8. Have a Facebook account (for identity validation to reduce duplicate attempts at enrollment); and
9. Be willing to provide contact information (phone number, email) to the study team.

8.2 Participant Exclusion Criteria

All individuals meeting any of the exclusion criteria at baseline will be excluded from study participation. Participants will be excluded if they:

1. Are unwilling or unable to provide informed consent.
2. Are unwilling to provide contact information (phone number, email address).
3. Report having a preliminary positive or positive HIV result in a test completed less than 30 days prior to the date of screening or report being currently under treatment for HIV infection.

8.3 Strategies for Recruitment and Retention

8.3.1 Recruitment

During the first phase of the project, the study team will develop culturally appropriate advertisement materials promoting HIV testing. The study aims to recruit participants from three distinct web-based platforms: social media sites (Facebook, Instagram, Twitter), dating apps (Grindr/alternative, Hornet, Jack'd) and informational sites (Google, Bing, Yahoo). These platforms will allow us to purchase advertisements and target the message to specific groups with particular characteristics (e.g., age, gender, location, etc.). Recruitment will occur in 3 waves: (1). Google, Facebook and Grindr/alternative, (2). Bing, Instagram and Jack'd, (3). Yahoo, Twitter and Hornet. Each wave will be open for 1 month to enroll at least 133 participants. The enrollment will stop if the wave hits the target sample size (N=133

kits ordered), otherwise might be extended beyond 1 month to achieve the target sample size.

A fixed and equal amount of funds and effort will be used to promote the study in the three types of study platforms to ensure similar promotion strategy. The advertisements on social media sites and dating apps will combine pictures and text promoting self-testing for HIV. Advertising on informational sites includes only text. To address the lack of visual aids that could attract participants in the study, we will adapt messages that will be used for to the social media sites/dating apps ads by properly formatting it (i.e., bold key-words of the phrase, such as “Free test kit”).

We will work with the Youth+Tech+Health (YTH) initiative of Education, Training, and Research (ETR), a nonprofit, science-based organization with significant experience working on youth health promotion campaigns and programs using the internet, social media and dating apps. Advertisements will be developed by ETR. The members of the ETR team have experience developing similar materials and an extended network of community partners that will ensure the advertisements and messages are acceptable by the study population.

ETR will create a set of graphics promoting HIV testing uptake (e.g., text containing “Free HIV test kits”), as well as a set of options of descriptive text to accompany the images. Those image and text combinations will be tested for use in the advertising campaign. The ad that will be in the final package for each platform for the advertisement campaign will be determined using A/B testing, which involves presenting two versions of proposed ads on an online platform while holding other variables (e.g., demographic targets, time of day) constant. The study team will not record and/or maintain any evaluable data arising from the above-mentioned process, as this is outside the scope of this study.

Promotion efforts will be focused on men aged 18-30 years (inclusive), with targeted advertisement in the regions defined by the site selection process. The online platforms do not allow for targeted advertisements towards race, ethnicity or sexual orientation. We will address this by adapting the screening questionnaire to exclude ineligible users. Advertisements will be displayed to users on specific days and times of the day in all three platforms based on utilization data from the specific platform. For example, dating apps may have more traffic during evening hours and informational sites may see higher utilization in the mornings. On informational sites, we will select specific keywords, such as “HIV,” “test,” “kit,” when the user types these keywords in the search box or conducts a search using a phrase that contains these keywords, the study ad will be displayed as part of the search results.

Upon clicking the advertisement banner posted on one of these platforms, users will be redirected to Qualtrics (the study informational page), where they will be informed about the study and complete the screening questionnaire. The screening questionnaire will evaluate each participant’s eligibility and it will be designed based on the inclusion/exclusion criteria listed above. This will take approximately 5 minutes. Only eligible participants will be asked to sign up to the study using their Facebook account and proceed to review the study information sheet. Signing up using Facebook and verifying the Facebook account has 10 friends will minimize duplicate entries. Non-eligible participants will be informed that they are not eligible for the study and provided with information on HIV prevention and PrEP, location of testing sites, and PrEP providers in their area.

Cognitively impaired participants, pregnant women, children or employee volunteers will not be included in the study as they do not belong to the study population. This study will only recruit MSM who identify as Latino and/or Black/African American.

During the active enrollment phase, we will record metrics such as impressions (the number of times

the ad is displayed) and click-through rate (the number of clicks generated per impression of a banner ad). This information will be recorded automatically by the website platforms and will help us in evaluating the success of each campaign. We will collect and store anonymized data from participants who undergo screening and are not eligible to participate.

8.3.2 Special Populations to Consider

This study will not target persons involved in the criminal justice system. The study will not assess prisoner status, and recruitment will not target persons that may be incarcerated/detained in a correctional facility; currently considered “prisoners” by local or state laws; parolees or probationers.

8.3.3 Retention

Our approach to succeed in reaching our enrollment target (approximately N=400 participants who order test kits) and ensure retention will include allocating sufficient staff time, providing an appropriate reimbursement to participants, and sending automated reminders about follow-up assessments via email to participants. At baseline, participants who provided contact information but did not complete all the questions on the questionnaire and/or those who did not provide their information to acquire a test kit may receive up to five reminder emails. During the follow-ups, each participant will receive up to five reminder emails that will encourage them to provide their test result and complete the follow-up questionnaire. Each participant will receive a $25 electronic gift card upon completion of each evaluation (baseline, 14-day follow-up, and 60-day follow-up) for a maximum total of $75.

9.0 SITE SELECTION

9.1 Recruitment Sites

9.1.1 Online Recruitment Platforms

All recruitment for this study will occur online with blast advertisements that will be purchased on **social media sites** (Facebook, Instagram, Twitter), **dating apps** (Grindr/alternative, Hornet, Jack'd) and **informational sites** (Google, Bing, Yahoo). We will recruit approximately 400 participants across all three platforms.

Website Characteristics and Rationale for Selection: For the purposes of this project, we selected websites that are popular among the study population (MSM, aged 18-30 years old) and allow us to place user-targeted and location-targeted advertisements. The study team's experience with using Facebook as an enrollment site was also a contributing factor in website selection.

Below we present the rationale for selecting each of the nine websites that will be used in this study.

Social Media Sites

Facebook is an American online social media and social networking service company based in Menlo Park, California. Facebook is a social networking website where users can post comments, share photographs and post links to news or other interesting content on the web, chat live, and watch short form video. It is accessible though the dedicated smartphone application or a regular browser, such as Internet Explorer. Facebook remains the primary social media platform for every American: two-thirds of U.S. adults (68%) now report that they are Facebook users, and roughly three-quarters of them access Facebook on a daily basis[13]. In addition, 81% of the U.S. adults aged 18-29 own and use a Facebook account[13]. Perhaps for these reasons, Facebook has been frequently used in many studies as a means for recruitment and prevention message dissemination[13]. Our team has previously used Facebook to recruit and retain MSM for the 12- month duration of one study[30].

Instagram is a photo-sharing social networking app that enables users to share pictures and video or slideshows. Users can access Instagram from their smartphone or tablets, as well as their browser. As of June 2018, the social network reported more than 1 billion monthly active users worldwide. In the United States, there are over 110 million active Instagram users. Overall, Instagram is one of the most popular mobile social apps worldwide with high levels of user engagement. Instagram is dominated by mostly by younger users below the age of 35, many of whom take an interest in gaining a glimpse into the lives of celebrities by following their individual Instagram accounts[31]. In a recent study, among focus groups of Black college students to understand dissemination of HIV testing campaigns and explore better approaches, participants indicated Instagram as one of the preferred social networks underscoring the increased popularity and usage of these particular sites for young people (18–29 years of age) and non-Hispanic blacks[22].

Twitter is an American online news and social networking service on which users post and interact with messages known as "tweets". There are over 69 million Twitter users in the U.S. and on average 36% of Americans aged 18 to 29 years old use Twitter[32]. Twitter has become an important tool for marketers and celebrities to connect with their respective audiences in real time.

Dating Apps

Grindr is the largest social networking app for gay, bisexual ("bi"), transgender ("trans") and queer people[33]. Grindr is mainly utilized to meet sex partners: a study among young MSM in Los Angeles showed that 29% of their participants use Grindr to meet sex partners ("hook up"). Grindr has an estimated 2.4 million daily active users and 6 million monthly users worldwide[34]. The site is accessible only via its dedicated smartphone application. Many studies have used Grindr as a platform to reach and recruit study participants. Our team has used Grindr for blast ads and has reached nearly 12,000 unique users, which resulted in 334 HIV self-test requests (out of which two participants reported a preliminary positive result)[6].

> *Note: Grindr was selected given its popularity with the study population. However, on 01/14/2020, Grindr stopped running advertisements on its self-service platform. This disruption resulted in the study advertisement not being run. As a result, the study team decided to pause Wave 1. While Wave 1 is paused, Waves 2 and 3 will be run. As of 4/29/2020, Grindr has resumed running advertisements, but the study team has also selected an alternate dating app, Scruff, that will be used if issues with Grindr re-emerge. Throughout the protocol, Grindr/alternative will be used to refer to the Wave 1 dating app to reflect that plans to proceed will vary based on Grindr's advertising status.*
>
> ***Scruff** (a potential alternative to Grindr) is a mobile application for gay, bisexual, and transgender men to connect with others. Users can upload photos and search for other users. Scruff has approximately 15 million global users[65].*

Jack'd is a location-based mobile app for gay, and bisexual men to meet other men. The app has a global network of 1.2 million users spanning 2,000 cities in 180 countries. Nearly 80% of its users are under 24 years, 30% of its users are Black and 20% multiracial or Latino[35].

Hornet combines online dating functions; the main website also supplies a platform where users can exchange stories and read LGBTQ+ news[27]. It has nearly 3 million users in the United States, the most active users are gay men ages 18-34 years. In the USA, Caucasians make up more than half of the members at 55%, followed by Latinos at 16%, then African-Americans at 9%[36].

Informational Sites

Google is an internet search engine used to find information on someone or something. According to Google, there are about 3.5 billion searchers per day and 1.2 trillion searchers worldwide[37]. The search engine can be accessed from personal computers or handheld devices, such as smartphones or tablets. Users that type in the search term they are looking for information on and the search engine provides suggested results. We plan on using terms such as "HIV," "test," and "HIV prevention," to name a few.

Bing is a web search engine owned and operated by Microsoft. It has the second highest market share among the leading mobile search providers in the United States only behind Google. Bing currently generates a monthly search volume of around 12 billion search requests worldwide as of August 2017[38]. Bing users are generally less tech savvy compared to Google users, and 40% was younger than 30 years old. Bing utilizes a similar approach to such as Google Ads[39]. Advertising can occur by using specific keywords, and can be targeted using location, language, demographics (age, gender). Messages can also be displayed on specific days/times.

Yahoo is a California-based, multinational technology company known worldwide for its search engine, Yahoo Search, and other services such as Yahoo web portal, News, and Mail. It is the third largest search engine in searches behind Google and Bing[40]. Advertising is similar to the previously

described search engines, using keywords with the ability to target the messages based on location or demographics.

9.1.2 Geographical Study Areas

We will place advertisements in 8 states and the District of Columbia (DC), all of which have high-incidence of HIV. In addition to **DC**, advertisements will be targeted to users in the states of **Florida, Georgia, Louisiana, Maryland, Mississippi, Nevada, South Carolina** and **Texas**.

Site characteristics and Rationale: The geographical areas included in the trial are expected to have a high frequency of MSM with an unknown status of HIV infection and high incidence of new HIV infections in the study population (MSM, aged 18-30 years old). According to the CDC "Get Tested" website (*www.gettested.cdc.gov*)[64], there are free or low-cost HIV testing and treatment services in these geographical areas that are available to assist participants who potentially will test positive for HIV infection or offer participants with alternatives to study participation[64]. Finally, we selected areas with sufficient PrEP providers or PrEP assistance programs, as well as states that have adopted expanded Medicaid/Medicare services to facilitate the uptake of PrEP among study participants [**Table 2**].

We selected states/territories with high rates (≥15 cases per 100,000 people) of new HIV cases among the population[2] [**Table 2**]. Among those states, we selected those that are in the "South," as defined by the U.S. Census Bureau and used in CDC's National HIV Surveillance System. In 2016, the South accounted for 53% (9,584) of the 18,160 new HIV diagnoses in the United States, followed by the West (17%; 3,129), the Northeast (17%; 3,088), and the Midwest (13%; 2,359)[41]. By focusing on these areas, we aim to provide a benefit to underserved local populations by offering a linkage to local HIV testing and PrEP. Additionally, we selected the states with high quality, free or low-cost care community clinics that participants can visit to receive treatment or testing for HIV and Sexually Transmitted Diseases.

Although some states (California and New York) meet the above criteria, we excluded them from this study due to the increased amount of resources for HIV testing and PrEP uptake in those states.

Participants will be encouraged to visit a PrEP provider. All participants will be sent links to websites (such as PrEPlocator.org and pleasePrEPme.org) that include information on PrEP and locations of PrEP providers by zip code across the U.S. Additionally, the study will recommend using the services of a telemedicine PrEP provider (PlushCare.com), a telemedicine provider that offers HIV/STD testing/ treatment and PrEP services in all 50 states.

Table 2: Site Selection Characteristics

State	Diagnoses of HIV in adults and adolescents (2016)[2]		Confirmatory test referral sites[63]	PrEP support services[64]	Medicare/ Medicaid Expansion	Identified as Study Site
	Number	*Rate (per 100,000)*				
Alabama	533	13.1	Yes	Yes	No	
Alaska	37	6.1	Yes	Yes	Yes	
Arizona	778	13.5	Yes	Yes	Yes	
Arkansas	314	12.7	Yes	Yes	Yes	
California	4961	15.2	Yes	Yes	Yes	
Colorado	423	9.1	Yes	Yes	Yes	
Connecticut	251	8.2	Yes	Yes	Yes	
Delaware	117	14.5	Yes	Yes	Yes	
DC	326	55.6	Yes	Yes	Yes	x
Florida	4940	28	Yes	Yes	No	x
Georgia	2709	31.8	Yes	Yes	No	x
Hawaii	82	6.8	Yes	Yes	Yes	
Idaho	44	3.2	Yes	Yes	Yes	
Illinois	1384	12.9	Yes	Yes	Yes	
Indiana	483	8.8	Yes	Yes	Yes	
Iowa	133	5.1	Yes	Yes	Yes	
Kentucky	141	5.9	Yes	Yes	Yes	
Louisiana	1151	29.7	Yes	Yes	Yes	x
Maine	50	4.3	Yes	Yes	Yes	
Maryland	1097	21.7	Yes	Yes	Yes	x
Massachusetts	710	12.1	Yes	Yes	Yes	
Michigan	747	8.9	Yes	Yes	Yes	
Minnesota	286	6.2	Yes	Yes	Yes	
Mississippi	424	17.1	Yes	Yes	No	x
Missouri	511	10	Yes	Yes	No	
Montana	17	1.9	Yes	Yes	Yes	
Nebraska	76	4.9	Yes	Yes	Adopted	
Nevada	525	21.4	Yes	Yes	Yes	x
New Hampshire	42	3.6	Yes	Yes	Yes	
New Jersey	1143	15.2	Yes	Yes	Yes	
New Mexico	125	7.2	Yes	Yes	Yes	
New York	2875	17.2	Yes	Yes	Yes	
North Carolina	1404	16.5	Yes	Yes	No	
North Dakota	46	7.4	Yes	Yes	Yes	
Ohio	969	9.9	Yes	Yes	Yes	
Oklahoma	293	9.1	Yes	Yes	No	
Oregon	221	6.4	Yes	Yes	Yes	

State	Diagnoses of HIV in adults and adolescents (2016)[2]		Confirmatory test referral sites[63]	PrEP support services[64]	Medicare/ Medicaid Expansion	Identified as Study Site
	Number	*Rate (per 100,000)*				
Pennsylvania	1150	10.6	Yes	Yes	Yes	
Rhode Island	70	7.7	Yes	Yes	Yes	
South Carolina	757	18.1	Yes	Yes	No	x
South Dakota	39	5.5	Yes	Yes	No	
Tennessee	715	12.8	Yes	Yes	No	
Texas	4464	19.8	Yes	Yes	No	x
Utah	135	5.7	Yes	Yes	Yes	
Vermont	8	1.5	Yes	Yes	Yes	
Virginia	893	12.6	Yes	Yes	Yes	
Washington	432	7.1	Yes	Yes	Yes	
West Virginia	66	4.2	Yes	Yes	Yes	
Wisconsin	224	4.6	Yes	Yes	No	
Wyoming	20	4.1	Yes	Yes	No	

10.0 STUDY PROCEDURES

10.1 Screening Visit

Study procedures (screening, baseline evaluation, follow-ups) will take place online on the participant's mobile device (e.g., smartphone, tablet) or computer. After following the link on the advertisement, users will land on the study informational page on Qualtrics, where they will receive brief information on the study (goal of the study, procedures, reimbursement information) and can choose to proceed with the eligibility screening process.

Interested users will sign in using their Facebook account. This is a single sign-on application which allows users to interact with other websites through their Facebook account and is used by many Facebook users in their daily web-based interactions. Facebook sign-on is similar to the "traditional" registration required to access or interact with many websites and it is frequently used in many popular sites[43]. Users will share with the study team their full name and email address. Our team has experience using this method for recruitment and validation of participation in previous studies.

Interested participants will fill out the eligibility/screening questionnaire, and an algorithm programmed using the study inclusion/exclusion criteria will determine each users' eligibility based on their responses. Eligible users will have to review the study information sheet and provide consent via checkbox before being enrolled in the study. Users who do not meet the eligibility criteria or do not agree to participate upon reviewing the informed consent will be referred to a website that contains information on HIV infection, STDs, testing locations, and PrEP.

10.1.1 Informed Consent Procedures for Participants

We anticipate obtaining a waiver of written consent from the IRB of Record for the eligibility screening, as this study is minimal risk and does not involve procedures for which written consent is normally required outside the research setting. Each potential participant will provide their consent electronically before being enrolled in the study. Due to the minimal risk associated with this study, an alteration of written informed consent will be requested from the IRB of Record for full study participation; an electronic study information sheet will be provided to eligible participants for review. The study information sheet will describe study procedures, participant rights, potential risks and benefits, as well as information on how to contact the research team members and IRB. Participants will declare their agreement to participate by clicking an "Agree" or "Disagree" button and proceeding to the baseline questionnaire. Users will also have the option to download a copy of the study information sheet on their phone, tablet or computer. If users decline to participate in the study, they will be redirected to a site with information about HIV and STD prevention, PrEP, and testing clinics, and their eligibility screening data will be collected and stored anonymously.

10.2 HIPAA Authorization and Medical Record Release Forms

Participants are providing authorization to share their information willingly by selecting "Agree" after review of the study information sheet. As this study is not collecting patient-specific data or information, participants will not be requested to sign a HIPAA authorization or Medical Release Form.

10.3 Baseline Assessment

The baseline assessment will take place after enrollment. During the baseline assessment, participants will provide their contact information (phone number, email address) and complete the baseline

questionnaire. Participants will then receive instructions on how to order their test kit and will also receive informational materials on HIV testing, PrEP and a link listing local HIV/STD testing locations and PrEP providers. All procedures will be completed online.

The baseline questionnaire will include basic demographic and contact information, questions on HIV risk assessment, HIV testing behavior, stigma, substance use (TAPS Tool), an evaluation of their Stage of Change (Transtheoretical Model of Change), and measure of sexual delay discounting. The baseline assessment will take approximately 20 minutes to complete.

Upon completion of the baseline assessment, participants will receive an email that will include a coupon code for a free HIV home self-test kit, instructions on how to order a home self-test kit, links with testing and PrEP sites. Participants will be instructed to use the coupon code on the OraSure.com website to place an order for a test kit. The test kit will be shipped by mail to the participant's home address in a discreet mailing package and will also include information materials on HIV, PrEP, and STDs. OraQuick® will be responsible for assembling and shipping the test kits using informational material provided by the study team. Test kits will be provided to the participants for free and the study will cover all related expenses.

Each participant will only be allowed to order one test kit. To avoid duplicate ordering, we will use the Facebook Single Sign On (SSO) feature as a validation method to confirm that each participant will have a unique account. A research assistant will review the name and email address of each participant before sending the coupon code for the HIV self-test kit. Additionally, each coupon code will be unique to each participant. This will allow us to confirm and track test kit ordering per the study's main outcome.

Within 72 hours after their participation, a research assistant will send an email to the participant that will include a list of brick-and-mortar clinics local to the participant where they can receive free HIV testing as well as PrEP services. Furthermore, participants will have the option to request online PrEP services through PlushCare.com, a web-based primary care medical provider that offers treatment for STDs, HIV, and laboratory testing via telehealth among its other services.

Finally, within 72 hours after their participation, a research assistant will email the participant a $25 electronic gift card, using the mailing address previously provided by the participant.

10.4 Intervention

Self-testing using the OraQuick® In-Home HIV Test kit: Each participant will be encouraged to order an HIV home test kit. We will use the OraQuick® In-Home HIV Test kit, a rapid test that detects antibodies to HIV on oral fluid in 20 minutes[44]. The test was approved by the FDA in 2012 for the use by adults 17 years of age or older. The kit is designed for use by untrained/non-medical users at home. The kit comes in a small case and includes a sample collection device (test stick), a test tube with liquid, and step-by-step instructions (in both English and Spanish) on how to perform the test. Briefly, the user collects the samples with the test stick by swiping their gums. Then, the user will place the test stick in the test tube that contains liquid. The test result must be read after 20 minutes. The kit includes detailed and pictorial information on the interpretation of the result. Additionally, the manufacturer provides a 24/7 support telephone number, where kit users can ask for assistance or testing sites to confirm their result.

Uptake of Pre-Exposure Prophylaxis: One secondary outcome of this intervention is uptake of oral pre-exposure HIV prophylaxis (PrEP). PrEP is an FDA-approved pill that contains a fixed- dose combination of tenofovir disoproxil fumarate and emtricitabine. It has been proven highly effective in preventing HIV in adherent, high-risk individuals and is well-tolerated[45-46]. Following completion of the baseline assessment, participants will be given information about the effectiveness of PrEP and will be

referred to providers that offer PrEP services. To facilitate uptake, we will email each participant links to two online directories of providers (PrEPlocator.org, pleasePrEPme.org), as well as a list of local community organizations and information about PlushCare.com, which offers telehealth services that include PrEP. As per CDC guidelines[46], people who wish to start PrEP must undergo risk assessment for acquisition of HIV infection, as well as a baseline clinical and laboratory evaluation that includes HIV and STD testing. Study participants will discuss their options with the healthcare provider of their choosing (local clinic, PlushCare.com, or their primary care physician). The study team will have no involvement in the clinical evaluation and decision for starting PrEP.

10.5 Premature Withdrawal of Participants

All participants will be followed for up to 60 days, unless they withdraw their consent, die, become unable to participate or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include but are not limited to: lack of funding, participant becomes incapacitated or enters a controlled environment prohibiting them from fully participating in the study (e.g., hospital admission), or early termination of the study for effectiveness reasons. Premature withdrawal of participants will occur at the discretion of the PI.

A research assistant will contact participants who were withdrawn or terminated from the study and recommend that they visit a local site for testing for HIV and/or PrEP. The team will use the provided contact information, preferably phone, and will attempt to contact each participant up to five times via follow-up calls.

10.6 Study Halting Rules

This is a minimal risk study and we do not anticipate any serious adverse events that could lead to the pause or early termination of the study. Participation in the study poses minimal risk to study participants. HIV self-testing was designed to be user friendly and is an acceptable, non- invasive and safe procedure; the sample (oral fluid) is collected by self-swabbing the user's gums. In the case of an initially positive HIV result, there is minimal risk of psychological discomfort upon learning one's result. Participants will have 24/7 support phone numbers at their disposal. Additionally, participants willing to initiate PrEP will have to undergo medical evaluation, including laboratory tests. Participants who start taking PrEP will be under medical care by their provider.

However, if data arise that the participant's health and/or welfare are put at risk, the PI will inform the IRB, and the sponsor through existing communication channels. The Monitoring bodies will determine on a case-by-case basis whether the participant will continue to be part of the study.

10.7 Follow-Up

Follow-up assessments will occur 14 days after completion of the baseline assessment, and again at 60 days post-baseline. Participants will be reminded via email or text message to participate in the follow-up assessment. Participants will have to participate within 7 days after the receipt of their first reminder. During those days, participants will receive daily automated emails or texts to participate in the follow-up assessments. Both the 14-day and 60-day assessments will be performed online.

During the first follow-up time point (14 days after the baseline assessment), participants will be asked to fill out an online questionnaire that will request information on HIV home self-test kit use, their test kit result and PrEP uptake. The assessments required at the 14-day follow-up are detailed in the Table of Assessments (Section 11.1). Participants will be requested to submit a photograph of their test kit result, which will be sent to a secure server. If this is not feasible or if they do not wish to share a

picture, they will be allowed to simply report their result. Participants who report a preliminary positive HIV result will receive information via email on local testing clinics and they will be encouraged to visit the clinics for confirmatory testing. A study team member will follow-up with them within 72 hours to discuss confirmatory testing. Participants with a negative result who report that they did not start PrEP will be asked the reasons for not starting PrEP (considering they reviewed the initial packet of PrEP information), their opinions on PrEP as a preventive measure, and their willingness to start PrEP. Finally, participants will be offered different options to acquire PrEP via email: a list of local brick-and-mortar clinics that provide PrEP or a voucher for PlushCare.com that can be redeemed for the initial PrEP appointment and laboratory testing. Participants who report an invalid or indeterminate HIV result will receive information via email on local testing clinics and they will be encouraged to visit the clinics for confirmatory testing. A study team member will follow-up with them within 72 hours to discuss confirmatory testing.

For the second follow-up time point (60-days post-baseline), participants will be asked to fill out a questionnaire that will vary depending on their responses to the 14-day follow-up. This questionnaire may include questions that request information on HIV self-test kit use, their test kit result, and PrEP uptake, if this information was not previously reported. The assessments at the 60-day follow-up are detailed in the Table of Assessments (Section 11.1). Participants who previously reported that they had not used the test kit will be inquired about using the kit, their result, and asked to submit a picture. As with the first follow-up visit, participants with a preliminary positive or invalid/indeterminate result will be encouraged to visit local clinics for testing. A study team member will follow-up with them within 72 hours to discuss confirmatory testing. Participants with a negative result who report that they didn't start PrEP will be asked the reasons for not starting PrEP (considering they reviewed the initial packet of PrEP information), their opinions on PrEP as a preventive measure, and their willingness to start PrEP. Finally, participants will be offered different options to acquire PrEP: a list of local brick-and-mortar clinics that provide PrEP or a voucher for PlushCare.com.

Within 72 hours from their participation after each follow-up assessment, a research assistant will email a $25 electronic gift card to the participant, using the contact information that was provided at Baseline.

10.8 Participant Reimbursement

Participants will be compensated upon the successful completion of the baseline assessment, and after each completed follow-up visit. Each participant will be emailed a $25 electronic gift card. During their participation in the study, participants may be compensated with a total of up to $75.

Participants who don't complete the requirements of each time point will not be compensated for the specific time point.

11.0 STUDY ASSESSMENTS

11.1 Table of Assessments

Measure	Screening	Baseline	14-Day Follow- up	60-Day Follow- up
Screening Questionnaire	x			
Demographics & Contact Information		x		
Social Media Activity		x		
Rapid HIV Behavioral Assessment		x		
Tobacco, Alcohol, Prescription medications, and other Substance use (TAPS) Tool		x		
The Transtheoretical Model of Health Behavior Change (Stage of Change)		x		
Attitudes Toward HIV Testing		x		
Reasons for Not Testing for HIV		x		
Attitudes Toward HIV Treatment		x		
Stigma Index		x		
Medical Mistrust		x		
Sexual Delay Discounting		x		
HIV Self-Test Result			x	x
PrEP Use			x	x
PrEP Uptake Facilitators & Barriers			x	x
PrEP Opinions			x	x
Study Evaluation Questions				x
OraQuick® Self-test Kit Orders		x	x	x
Website metrics	x	x	x	x

11.2 General Measures

11.2.1 Screening Questionnaire

This form asks a number of questions specifically related to the eligibility criteria previously described in this protocol. The questionnaire is designed to evaluate each potential participant's eligibility for the study. Participants will have to fill out this questionnaire at the beginning of the study, before informed consent and enrollment. Only participants who meet study eligibility criteria will be allowed to continue with enrollment.

11.2.2 Demographics and Contact information

This form collects information about demographic characteristics of the participant, including gender, date of birth, ethnicity, race, education. This form is completed at baseline only.

11.3 Measures of Primary and Secondary Outcomes

11.3.1 Social Media Activity

These questions will measure social media sites participants belong to, the number of hours they spend using social media, and the reasons why they use social media. These questions were used by Young et al.[30] as part of the HOPE study. Participants will fill out these questions during the baseline assessment.

11.3.2 Rapid HIV Behavioral Assessment

Rapid HIV Behavioral Assessment (RHBA) is a method for collecting information about sexual, drug-use, and HIV testing behaviors from people at high risk for HIV infection in areas with low- to-moderate HIV prevalence[47]. For the purposes of this study, we will use a subset of the sexual behavior questions to estimate the risk of study participants. This tool will include approximately 5 questions on number of sex partners, condom use, and if they practice anal sex.

11.3.3 Tobacco, Alcohol, Prescription Medications, and Other Substance Use Tool

The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool is a two-part screening and assessment tool with between 3-27 items. Part 1 features a 3-item screening for tobacco, alcohol, prescription medication, and illicit substance use in the past year. The TAPS Tool also contains a brief assessment (up to 24 questions) of a person's past 30-day use to detect substance use, sub-threshold substance use disorder (i.e., at-risk, harmful, or hazardous use), and substance use disorders[56]. Because this measure will not address the study's primary outcome, sections on tobacco use will be removed from the tool. Participants will complete this measure as part of the baseline assessment.

11.3.4 The Transtheoretical Model of Health Behavior Change (Stage of Change)

The Transtheoretical Model of Health Behavior Change (Stage of Change) (TTM) consists of one-question that focuses on the decision-making of the individual and is a model of intentional change. The TTM operates on the assumption that people do not change behaviors quickly and decisively. Rather, change in behavior, especially habitual behavior, occurs continuously through a cyclical process. The participant responses will be categorized in one of the following six stages: pre-contemplation (not intending to change), contemplation (intending to change within 6 months), preparation (actively planning change), action (overtly making changes), and maintenance (taking steps to sustain change)[48]. For this study, participants' stage of change associated with HIV testing will be assessed. Participants will respond to this question during the baseline assessment.

11.3.5 Attitudes Toward HIV Testing

The Attitudes Toward HIV Testing questionnaire evaluates the stance of participants towards testing for HIV. It was developed by Kalichman et al.[49]. Participants will respond dichotomously (agree or disagree) to approximately five items. Two items reflect positive outcomes from testing, two assess

adverse outcomes, and one item reflects HIV testing avoidance. This measure will be part of the baseline assessment.

11.3.6 Reasons for Not Testing for HIV

Reasons for not testing for HIV will be measured via a one-question item extracted from the HIV Testing Questions - CDC (CHTQ), evaluating reasons for not testing. The tool was developed by the Centers for Disease Control and Prevention HIV-STD Behavioral Surveillance Working Group[50]. This question is part of a set of three Core Measures (Sexual Behavior, Drug-related HIV risk, HIV testing) developed by the CDC to standardize collection of data on HIV risk and preventive behaviors. This is version 9.00 of these questions. Participants will answer this question during the baseline assessment.

11.3.7 Attitudes Toward HIV Treatment

The Attitudes Toward HIV Treatment measure includes approximately 10 statements concerning Highly Active Antiretroviral Therapy (HAART)-related beliefs. They were evaluated by Stolte et al.[51]. Participants will respond to each statement using a 7-point scale ranging from 1 “strongly disagree” to 7 “strongly agree.” Participants will answer these questions during the baseline assessment.

11.3.8 Stigma Index

This measure includes approximately 4 questions[52] that will be combined to create the stigma index. The index uses a 7-point Likert scale, ranging from (1) completely disagree to (7) completely agree. Participants will answer these questions as part of the baseline assessment.

11.3.9 Medical Mistrust

Medical mistrust will be measured using the Medical Mistrust Inventory (MMI)[53], which assesses feelings of discomfort and suspicion that one has toward healthcare personnel and pharmacological treatment. The MMI is an approximately 7-item questionnaire that uses a 5-point Likert-type scale response key, ranging from (1) strongly disagree to (5) strongly agree. Participants will answer these questions as part of the baseline assessment.

11.3.10 Sexual Delay Discounting

Sexual delay discounting reflects an individual’s level of sexual impulsivity and will be measured using a modified version of the Sexual Discounting Task[54], which assesses the participant’s likelihood of waiting for a delayed condom relative to having immediate sex without a condom. Participants respond on a 101-point visual analogue scale to rate the likelihood of immediate unprotected sex versus delayed protected sex across approximately 8 time-points (e.g., now, 1 hour, 3 hours, 6 hours, 1 day, 1 week, and 1 month). Participants will answer these questions as part of the baseline assessment.

11.3.11 HIV Self-Test Result

Each participant will order an HIV home test kit to test for HIV. We will use the OraQuick® In- Home HIV Test kit, a rapid test that detects antibodies to HIV on oral fluid in 20 minutes. The test was approved by the FDA in 2012 for use by adults 17 years of age or older. The kit is designed for use by untrained/ non-medical users at home. The kit comes with laptop case that includes a sample collection device (test stick), a test tube with liquid, step-by-step instructions (in English and Spanish) on how to perform

the test. Briefly, the user collects the samples with the test stick by swiping their gums. Then, the user needs to place the test stick in the test tube that contains liquid. The test result must be read after 20 minutes.

This will include approximately 8 questions that will ask participants about whether the test kit was used, their result (positive, negative, invalid), and to upload a picture of the result. If their result is negative, they will be asked about PrEP (see 11.1.12), or if their result is “Positive” or “Invalid”, we will ask participants if they sought confirmatory testing. If so, participants will be asked to provide information about the type of provider, and if this information is not provided by the participant, they will receive a link with resources, such as clinics they can visit for testing.

Participants will have the opportunity to report their result during the 14-day follow-up and/or the 60-day follow-up. They will be asked to upload a photograph of their result on a secure online platform. If this is not feasible, they will be asked to provide their interpretation of the test result. The photograph will be interpreted by the study team and an alpha/numeric code will be entered into the database; the photograph will then be deleted. Participants will answer this question as part of the follow-up assessments.

11.3.12 PrEP Use

Participants will answer approximately four questions as part of the follow-up assessments. Participants will be asked if they reviewed the prevention materials included in the test kit and the email that was sent to them, if they visited a provider to discuss about PrEP or if they started PrEP.

11.3.13 PrEP Uptake Facilitators and Barriers

This tool will be used to collect perceived obstacles in starting PrEP. The questions are a modified version of a questionnaire developed by Golub et al.[55] and include approximately 19 questions in total. The questionnaire is divided into approximately 11 questions on “Barriers” and approximately 8 questions on “Facilitators” toward starting PrEP. Participants will answer these questions as part of the follow-up assessments.

11.3.14 PrEP Opinions

Participants will report their agreement or disagreement with approximately 19 statements about opinions on PrEP and PrEP use.

11.3.15 Study Evaluation Questions

Participants will answer approximately 13 questions related to evaluation of the study activities, such as the acceptability and desirability of online HIV self-test kit ordering and PrEP.

11.3.16 OraQuick® Test Kit Orders

Data addressing the primary outcome will not be assessed with participants, but will instead be reported by the product manufacturer, OraSure. OraSure will provide information on vouchers claimed by study participants; the research team will then link information on the claimed voucher to the participant within the study database (linking will be done by voucher number, no identifiable information will be sent by OraSure).

11.3.17 Website Metrics

We will record metrics, such as impressions (the number of times the ad is displayed) and click-through rate (the number of clicks generated per impression of a banner ad). This information will be recorded automatically by the website platforms and it will be part of the advertisement campaign. These metrics will help us evaluate the success of each advertisement campaign.

12.0 TRAINING REQUIREMENTS

12.1 Overall

A comprehensive Training Plan will be developed to incorporate general training, study-specific training, mechanisms for competency assessment as well as a detailed description of training, supervision, and fidelity monitoring procedures. The Investigative Team is responsible for the development of a comprehensive Training Plan, instructional material, and delivery of the training, with the team comprised of the Lead Node, Clinical Coordinating Center (CCC), Data and Statistics Center (DSC) (as applicable), as well as other participating nodes and subject matter experts, as applicable.

The CTN-0083 study staff will be trained as specified in the study Training Plan. Training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP) as well as protocol- specific training on assessments, study follow-ups and procedures, data management, quality assurance, etc. The Lead Node is primarily responsible for development and delivery of study- specific training related to the study intervention(s) and procedures, as well as data management. In collaboration with the Lead Team, the CCC is responsible for the development and delivery of non-intervention training, including regulatory procedures, quality assurance, monitoring, etc. Other parties will contribute as needed based on the subject matter and material to be covered. The various sub-teams will collaborate to deliver quality instructional material designed to prepare research staff to fully perform study procedures based on the assigned research roles and responsibilities.

In addition to general and study-specific training, the Training Plan will include a description of the delivery methods to be used for each training module (e.g., via self-study, online, webcast, or teleconference). Study staff is required to complete institutionally required training per their research site, Institutional Review Board(s), and authorities with regulatory oversight. Tracking of training completion for individual staff as prescribed for assigned study role(s) will be documented, endorsed by the site Principal Investigator and the Lead Node, and audited by the CCC. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

13.0 CONCOMITANT THERAPY/INTERVENTION

13.1 General

Participants of this study must not be taking PrEP at the time of their enrollment or in the 6 months prior to the date of enrollment. Additionally, participants must not be diagnosed with HIV infection or under treatment for HIV infection at the time of the baseline evaluation. The screening algorithm will include questions to ensure that participants on PrEP or HIV treatment are excluded from the study. Other medications and/or interventions are permitted.

13.2 Medications Prohibited/Allowed During Trial

There are no restrictions on medications that are prohibited or allowed during the trial.

14.0 STATISTICAL DESIGN AND ANALYSES

14.1 General Design

This is an observational study where participants will be recruited from three types of promotional platforms (social media sites, informational sites, and dating apps) to evaluate the effectiveness of the platforms in promoting HIV self-testing.

14.1.1 Study Hypothesis

The study will evaluate the relative effectiveness of using social media sites (i.e., Facebook, Instagram, Twitter), informational sites (i.e., Google, Bing, Yahoo), and dating apps (i.e., Grindr/alternative, Hornet, Jack'd) to promote self-testing of HIV infection among MSM who are at increased risk of HIV exposure and/or infection.

14.1.2 Primary and Secondary Outcomes Measures

Primary Outcome Measures

The primary outcome is the number of HIV home self-test kits ordered per day (number of study participants ordering an HIV home self-test kit per day) by promotional platform (social media, informational, dating sites). Without loss of generalizability, the primary outcome can also be defined as the number of HIV home self-test kits ordered per a given period via a simple transformation. For example, one can calculate the number of kits ordered per 30 days, per 100 days, etc. The number and timing of HIV self-testing kit orders will be recorded and analyzed to evaluate the effectiveness of the sites in promoting HIV self-testing. We assume that it will be rare for participants to order multiple copies of kits. If this occurs, we will analyze only the first occurrence.

Secondary Outcome Measures

The following secondary outcomes will be analyzed.

1. The number of participants who used the study-provided HIV home self-test kit by 60- day follow-up.
2. The number of participants who tested positive for HIV using the study-provided home test kit by 60-day follow-up.
3. The number of participants who reported a high-risk substance abuse profile at baseline who ordered an HIV home self-test kit.
4. The number of participants who reported a high-risk substance abuse profile at baseline who reported seeking PrEP services or started PrEP at either follow-up.
5. The number of participants in the "Determination" stage of change at baseline who ordered an HIV home self-test kit.
6. The number of participants in the "Determination" stage of change at baseline who reported seeking PrEP services or started PrEP at either follow-up.
7. The number of participants who tested positive for HIV using the study-provided home test kit and were linked to care within 30 days after self-testing.
8. The number of participants who tested positive for HIV using the study-provided home test kit and started treatment within 30 days after self-testing.

9. The number of participants who tested negative for HIV using the study-provided home test kit and sought PrEP services within 30 days after self-testing.
10. The number of participants who tested negative for HIV using the study-provided home test kit and started PrEP within 30 days after self-testing.
11. The amount of money spent per test kit ordered per promotion type, including all the costs of the intervention (advertisement, test kit).
12. The proportion of people from each website and the proportion of people from each type of website who clicked on advertisements.
13. Kit ordering rates expressed as kits ordered per unique participants visiting the website. This can be calculated using the same approach as in the primary analysis, except that we will use number of visiting participants rather than time as the offset. As in the primary analysis, we assume that it will be rare for participants to order multiple copies of kits, although visits to multiple websites may be more common. If there are one or more orders within a wave, we will use only the first order, together with its website. If there are multiple websites with no orders, we will use the first website.
14. The number of participants with high rate of sexual delay discounting at baseline who ordered an HIV home self-test kit.

14.1.3 Recruitment

Study participants will be recruited from three promotional platforms (social media sites, informational sites, and dating apps). Advertisement materials will be placed on the sites for the targeted population across 8 states and 1 territory (DC). The number of times the link to the eligibility questionnaire is accessed (click-through rate) will be tracked. Advertisements will display to users on specific days and times of the day. Upon clicking on the banner, users will be forwarded to a brief screening questionnaire that will evaluate their eligibility. We estimate that approximately 400 participants across the three promotional platforms will be enrolled over the recruitment period and order HIV self-test home kits.

14.1.4 Randomization and Factors for Stratification

This is not an intervention study; participants will not be randomized.

14.2 Statistical Methods for Primary Analysis

The promotional platforms and their planned implementation are provided below in Table 3. There are rows corresponding to times, and 3 columns: A, B, and C, corresponding to three types of promotional platforms (informational sites, social media sites, and dating apps). The study will recruit approximately 400 participants across the three waves. To conduct power calculations, we assume that the study will run until approximately 133 HIV home self-test kits are ordered to row 1 of Table 3, then 133 new HIV home self-test kits ordered to row 2 and finally, 133 new HIV home self-test kits ordered to row 3. Note that, some waves may not achieve 133 kits orders during the allotted time while others may surpass this number since multiple kits may be ordered the same day as the 133rd and platforms cannot be shut down in real time. All kits ordered while the wave is actively recruiting will be included in the primary outcome analysis.

Table 3: Study Data Layout: A = Informational sites, B = Social Media sites, C = Dating apps

	A	B	C
Wave 1	Google	Facebook	Grindr/alternative
Wave 2	Bing	Instagram	Jack'd
Wave 3	Yahoo	Twitter	Hornet

Analysis model

We assume that, for a given time period i, the numbers of kits ordered from sites $i1, \ldots i3$ will be given by three independent Poisson processes with rates $\lambda_{i1}, \ldots, \lambda_{i3}$. Time period i lasts until ~133 kits have been ordered, which will take time t_i.

The primary analysis model will thus be a Poisson regression model using time as an offset, in which:

$$log(o_{ij}) = log(t_i) + \alpha + \beta_i + \gamma_j + \beta\gamma_{ij}$$

where

- o_{ij} is the number of kits ordered by the site in row ii (i.e. time period ii), column jj
- t_i is the time that the Wave platforms were recruiting (i.e., ~133 participants recruited)
- β_i is the main row (wave) effect
- γ_j is the main column (promotional site series) effect
- $\beta\gamma_{ij}$ is the row-column interaction term Under this model, the rate for any site $iijj$ is given by:

$$rate_{ij} = exp(\alpha + \beta_i + \gamma_j + \beta\gamma_{ij})$$

In addition to the 9 individual rate estimates with their confidence intervals, it is interesting to know whether the 3 rates in a particular column are the same, and, if so, what the pooled rate estimate and its confidence interval are for that column. These questions can be addressed by SAS contrast and estimate statements. On the theory that lumping (i.e., pooling rates in a column) when you should split is worse than splitting when you should lump, multiplicity adjustments are undesirable, since increasing skepticism about p-values leads to lumping. Therefore multiplicity adjustments are not made on the 3 p-values (one for each column).

SAS Snippet

We show below the SAS code necessary to estimate the primary model, and contrasts and estimate statements that perform the analyses we selected for investigation in the simulation. These analyses, described in the simulation section, were selected because they were identified as ones of interest.

```
data long;
      set simul; lt = log(t); run;

proc genmod data = long;
      class row col;
```

```
model o = row | col / dist = poisson link = log offset = lt type3;

estimate "rate(1,3)" intercept 1 row 1 0 0
              col 0 0 1 row*col 0 0 1
                                          0 0 0
                                          0 0 0;

estimate "Pooled column 3 rate" intercept 3 row 1 1 1
              col 0 0 3 row * col    0 0 1
                                          0 0 1
                                          0 1 / divisor = 3;

contrast "H0: we can pool rates in column 3"
              row 1 -1 0 row*col 0 0    1
                                          0 0 -1
                                          0 0  0,

              row 1 0 -1 row*col 0 0    1
                                          0 0  0
                                          0 0 -1;
estimate "H0: col 2 = col 3"
              col 0 3 -3 row * col 0     1 -1
                                          0    1 -1
                                          0    1 -1 / divisor =
3;
                                    run;
```

14.3 Rationale for Sample Size and Statistical Power

Below, we present simulations demonstrating power and confidence interval width for selected aspects of the simulated data, as reflected in three series. Each series incorporates a parameter λ. Note that, some waves may recruit within less than a month or go beyond one month. The time it takes waves to recruit will be added in the model as an offset factor. Without loss of generalizability, for the purposes of the power calculations we assume that, each wave will recruit 133 participants in 1 month (i.e. 4 weeks), and set $\lambda = 66$ participants per 2 weeks for all three series, implying that we expect the recruitment goal of 133 participants will be accomplished in 1 month for each row of the experimental design.

We investigate the following sets of bi-weekly Poisson rates for the sites:

Series A:λ $\begin{bmatrix} (1\text{-}p)/2 & (1\text{-}p)/2\ p \\ (1\text{-}p)/2 & (1\text{-}p)/2\ p \\ (1\text{-}p)/2 & (1\text{-}p)/2\ p \end{bmatrix}$ *,where* $0 \le p \ge 1.$ For example when p= ½ ,this gives

$\begin{bmatrix} 16.5 & 16.5 & 33 \\ 16.5 & 16.5 & 33 \\ 16.5 & 16.5 & 33 \end{bmatrix}$ Kits ordered per 2 weeks

Series B:λ $\begin{bmatrix} (1\text{-}p)/2 & (1\text{-}p)/2 & p \\ (1\text{-}p)/2 & p & (1\text{-}p)/2 \\ p & (1\text{-}p)/2 & (1\text{-}p)/2 \end{bmatrix}$. For example when p= ½ ,this gives

$$\begin{bmatrix} 16.5 & 33 & 33 \\ 16.5 & 33 & 16.5 \\ 33 & 16.5 & 33 \end{bmatrix}$$ Kits ordered per 2 weeks

Series C: $\frac{\lambda}{1+\alpha+\alpha^2}\begin{bmatrix} 1 & \alpha & \alpha^2 \\ 1 & \alpha & \alpha^2 \\ 1 & \alpha & \alpha^2 \end{bmatrix}$ *,where* $\alpha > 0.$ For example when a=2, this gives roughly

$$\begin{bmatrix} 9 & 19 & 38 \\ 9 & 19 & 38 \\ 9 & 19 & 38 \end{bmatrix}$$ Kits ordered per 2 weeks

Below we show simulation results for four aspects of the data. We selected these aspects because we felt they are typical of the kinds of analyses that would be of interest.

- Figure 1 shows, selecting Grindr/alternative as an example of one the nine sites of interest, the mean estimated rate for Grindr/alternative and a region such that at least 80% of the 95% confidence intervals lie completely within this region.
- Figure 2 presents the mean estimated rate for column 3 margin (i.e., Dating Apps) and a region such that at least 80% of the 95% confidence intervals lie completely within this region (for series B, this is invalid and will not be performed.)
- Figure 3: Power of the test of the null that the rates within column 3 may be pooled (we expect good power only for series B.)
- Figure 4: Power of the test of the null that the pooled rates of columns 2 and 3 are the same (for series B, this is invalid and will not be performed.)

All power estimates are two-tailed at $\alpha = 0.05$. Assuming that our simulation represents the real world, we can draw the following conclusions about power and precision:

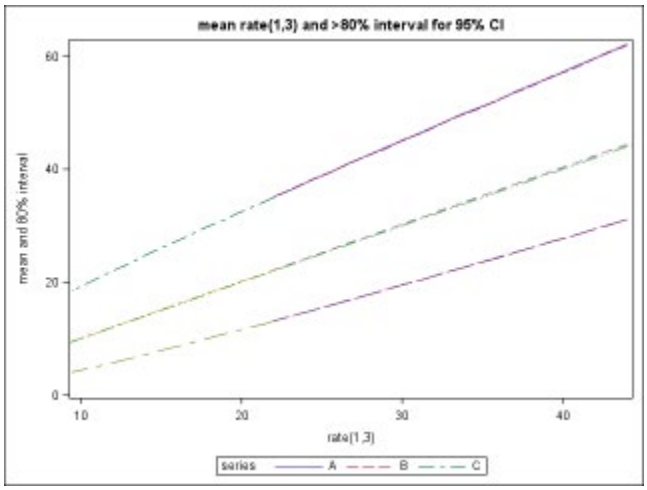


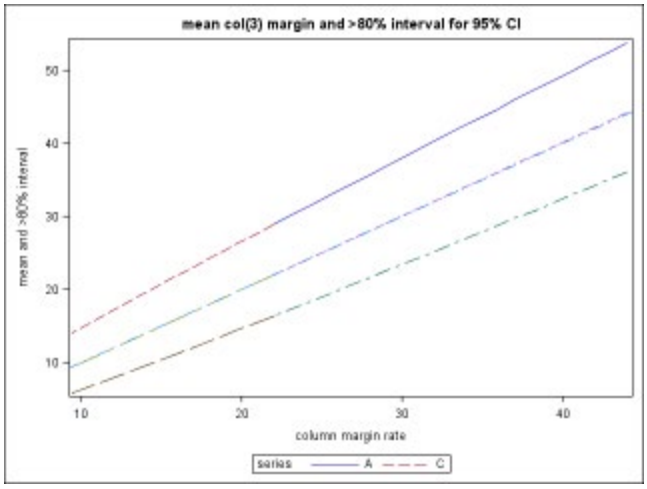
Figure 1: Mean estimated rate for Grindr/alternative (as an example) and a region such that at least 80% of the 95% confidence intervals for the Grindr/alternative rate lie completely within this region

There appear to be only three set of lines in Figure 1 because the results of the three series are plotted

on top of each other. The lower line in Figure 1 is the 10th percentile of the distribution of lower 95% confidence limits for Grindr/alternative, while the upper line is the 90th percentile of the distribution of upper 95% confidence limits. It can be shown (Appendix C) that at least 80% of the confidence limits for Grindr/alternative lie completely within this region. Thus, for example, if the true value for Grindr/ alternative is 40 kits per 2 weeks, it is very likely that the 95% confidence interval will lie completely within roughly (31,62). If the true value of Grindr/alternative is 10 kits per 2 weeks, the 95% confidence interval will probably lie completely within roughly (4,19).

The middle line shows the mean estimated rate of Grindr/alternative. There is another line in Figure 1 – the diagonal line from (10,10) to (40,40). It is not visible in Figure 1 because it is over-plotted by the middle line. This means that the estimate for Grindr/alternative is unbiased. These results seem not to depend on series.

Figure 2: Mean estimated rate for column 3 margin (i.e., Dating Apps) and a region such that at least 80% of the 95% confidence intervals for the column 3 margin lie completely within this region



There appear to be only three set of lines in Figure 2 because the results of the three series are plotted on top of each other. The lower line in Figure 1 is the 10th percentile of the distribution of lower 95% confidence limits for the column 3 (Dating Apps) margin, while the upper line is the 90th percentile of the distribution of upper 95% confidence limits. It can be shown (Appendix) that at least 80% of the confidence limits for the column 3 margin lie completely within this region. Thus, for example, if the true value of col (3) is 40 kits per 2 weeks, it is very likely that the 95% confidence interval will lie completely within (36, 54). If the true value of col (3) is 10 kits per 2 weeks, the 95% confidence interval will probably lie completely within roughly (4,15).

The middle line shows the mean estimated col (3) rate. There is another line in Figure 2 – the diagonal line from (10,10) to (40,40). It is not visible in Figure 2 because it is over-plotted by the middle line. This means that the estimate for the col (3) rate is unbiased. These results seem not to depend on series.

Because column 3 is not poolable in series B, no estimate or confidence interval has been presented for series B it, on the assumption that a poolability test will preclude their calculation.

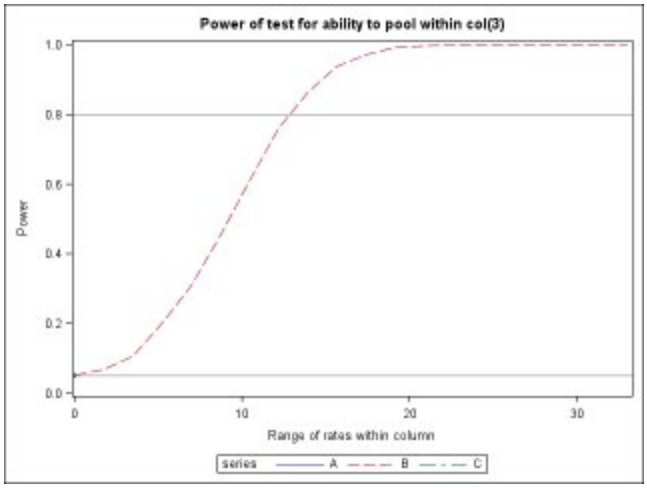


Figure 3: Power of the test of the null that the rates within column 3 may be pooled

Figure 3 shows that, in series B, we expect power better than 0.8 if the range of the cell-specific rates within column B exceeds about 12 kits per 2 weeks. When the range in series B is 0 (i.e., if p = 1/3) the type I error rate is 0.05, as desired. For series A and C, all the cell-specific rates within a column are always the same (i.e., their range is 0), so these series are represented in Figure 3 by a dot at (rate range, power) = (0, 0.05), showing that, as desired, the type I error for the poolability tests in these series is controlled at 0.05.

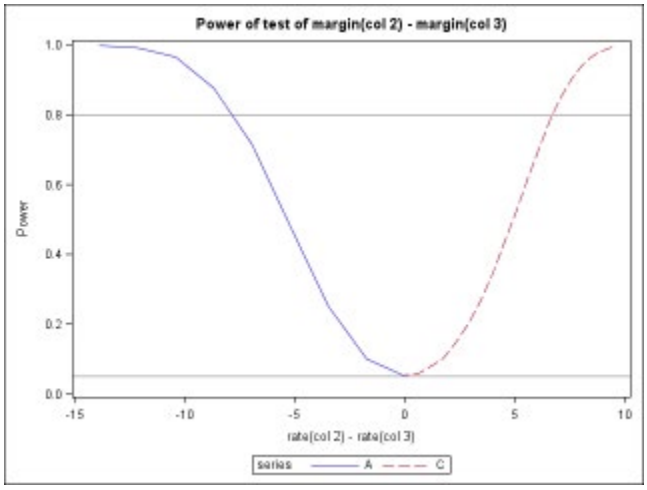


Figure 4: Power of the test of the null that the pooled rates of columns 2 and 3 are the same

Figure 4 shows that we expect power better than 0.8 for the test of equality between the marginal rates in columns 2 and 3 if the absolute difference (col 2 – col 3) exceeds 6 kits per 2 weeks in series C and 8 kits per 2 weeks in series C. Because columns 2 and 3 are each not poolable in series B, no confidence test has been presented for the marginal difference in series B, on the assumption that poolability tests will preclude its calculation.

14.4 Interim Analysis

No interim looks at primary or secondary outcomes are planned for this study.

14.5 Secondary and Exploratory Analysis

Secondary and exploratory analyses will be conducted using univariate tests and descriptive statistics such as counts, percentages, and 95% confidence intervals.

14.6 Missing Data and Dropouts

There will be no missing data or dropouts for the primary outcome since only participants who meet eligibility criteria and order HIV home self-testing kits will be included in the analysis. The primary outcome is the number of participants ordering an HIV self-test kit through the three promotional platforms. This information is automatically tracked in the system and should not be any missing data. For secondary outcomes, missing data can arise if a participant orders the HIV self-testing kit at baseline but misses the 14-day or 60-day follow-up visit. Every effort will be done to minimize missing data and dropouts. At baseline, participants who haven't completed all the questions of the questionnaires and did not provide their information to order a test kit will receive up to three automated reminder emails. During the follow-up visits, each participant will receive up to five automated reminder emails that will encourage to provide their test result and complete the follow-up assessment.

14.7 Demographic and Baseline Characteristics

Participant's baseline demographics and characteristics will be presented using summary statistics. Descriptive summaries of the distribution of continuous variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies/counts and percentages.

14.8 Safety Analysis

The study will not conduct a safety analysis, as this is not part of the objectives of the study. Potential risks associated with the study is learning he/she is HIV positive or breach of confidentiality. Only adverse events directly related to learning of HIV positive status will be captured in the database. AEs, including SAEs will be presented as: (1) the number and proportion of participants experiencing at least one incidence of each event overall; and (2) the total number of each event overall in tabular form. Detail in these listings will include severity and action taken, as available.

15.0 REGULATORY COMPLIANCE, REPORTING AND MONITORING

15.1 Statement of Compliance

This trial will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonisation Good Clinical Practice (GCP) Guidelines, applicable United States (US) Code of Federal Regulations (CFR), the NIDA Terms and Conditions of Award, and all other applicable state, local, and federal regulatory requirements. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a reference guide and study quality assurance tool.

15.2 Institutional Review Board Review and Approval

Prior to initiating the study, participating site investigators will obtain written approval from the Ethics Review Committee (ERC) or Institutional Review Board (IRB) to conduct the study at their respective site, which will include approval of the study protocol. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials, and any materials given to the participant, and any changes made to these documents throughout study implementation. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator is responsible for maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the investigator prior to the initiation of research activities at the site, and must be available at any time for audit. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

Annual progress reports and local Serious Adverse Event (SAE) reports, though expected to be rare, will be submitted to the IRB of Record. Annual reports and progress reports will be submitted to the IRB annually so that continuous study approval is maintained without lapse. The lead PI is responsible for maintaining in his research files copies of current IRB approval notice(s), IRB- approved consent document(s), including approval for all protocol modifications. These materials must be received by the Lead PI prior to the initiation of research activities at a given site and must be available at any time for audit.

The UCLA IRB will be the IRB of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating institutions have agreed to rely on the UCLA IRB and have entered into reliance/authorization agreements for Protocol CTN 0083. The UCLA IRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution.

15.3 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. Informed consent continues throughout the individual’s study participation. The informed consent form(s) will include all

of the required elements of informed consent and may contain additional relevant consent elements and NIDA CCTN specific additional elements. The study site must have the study informed consent form(s) approved by the IRB of record. Prior to initial submission to the IRB and with each subsequent consent revision, the consent form(s) must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) to confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(b), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(c) and any applicable CCTN requirements. Participants will review a study information sheet, which will include all of the required elements of informed consent, prior to completing the baseline assessments. Since participants will be asked to complete a screening questionnaire prior to completing the informed consent, the site will request a waiver of signed informed consent from the IRB of Record for screening purposes only. The study team will provide the participants with a study information sheet. The Lead site will have the study information sheet approved by its IRB. A copy of the IRB-approved study information sheet, along with the IRB study approval, must be sent to the Lead Node (LN) and the Clinical Coordinating Center (CCC) prior to the site initiation visit and with each subsequent consent revision. Every study participant is required to review an IRB-approved current version of the study information sheet prior to the initiation of the baseline assessment. Every study participant will be able to download a copy of the signed consent form for his record.

When an interested participant clicks on the ad, he will be brought to an informational page for the study in Qualtrics. The page will include information about the study and study contact information (email, phone number). Participants will be able to contact a research staff member, who will be able to answer any questions about the study. All persons providing clarification to potential study participants must have completed appropriate training. Participants will verify their agreement to participate by clicking on the “Agree” button at the end of the information sheet and proceeding with study activities.

The study information sheet must be updated or revised whenever the protocol is amended in a way that may affect participants’ participation in the trial. The participant will be informed that their participation is voluntary, and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be offered information regarding HIV prevention, including a list of low-cost sexual health clinics and PrEP providers and they will be encouraged to get tested for HIV. No source documents will be kept related to consent.

15.4 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. Qualified monitors will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation auditing, and evaluating whether the informed consent process is being correctly followed and documented. Non-conformity with protocol and federal regulations will be reported as a protocol deviation and submitted to the study sponsor and study IRB for further review.

15.5 Participant and Data Confidentiality

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency, and will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and

regulations. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency and the participant.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in Section 15.11, Records Retention and Requirements.

By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

15.5.1 Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). This protects participants from disclosure of sensitive information (e.g., drug use). It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

15.5.2 Health Information Portability Accountability Act (HIPAA)

The study will not require participants to sign a HIPAA release form.

The study does not preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. It is in conformance with 42 CFR 2.52, which allows for research-related provisions with regard to the disclosure of substance use disorder patient identifying information in the absence of the informed consent process and HIPAA authorization.

15.6 Investigator Assurances

UCLA has filed a Federal Wide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects in alignment with 45 CFR 46, Subpart A, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103). Prior to initiating the study, the Principal Investigator at the study site (UCLA) will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

15.6.1 Financial Disclosure/Conflict of Interest

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

15.7 Clinical Monitoring

The study team will meet regularly to discuss recruitment, retention, clinical questions, data collection, adverse events, and other study monitoring and management processes. Monitoring of the study site(s) will be conducted using a combination of NIDA CCTN CCC Monitors and qualified node personnel (Node Quality Assurance (QA) monitors) that will perform visits (remote or in person) at least once during each year or at a frequency requested by the study sponsor. This visit will include a review of protocol procedures and an audit of source documentation, including electronic informed consent forms and HIPAA forms (both as applicable), to help prevent, detect, and correct problems. Monitors will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the monitor's review of study documentation indicates that additional training of site study personnel is needed, the appropriate party will undertake or arrange for that training.

QA monitors will provide site management for each site during the trial. Node QA staff or other designated party(ies) will audit trial progress such as protocol deviations, adverse events, reporting requirements, and regulatory documentation. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. NIDA CCC Monitors and Node QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. Details of the contract for NIDA CCTN CCC Monitoring, node QA and data monitoring are found in the study Manual of Operating Procedures (MOP).

15.8 Inclusion of Women and Minorities

The study team will take steps to enroll a diverse study population, however, the study will not recruit women. We aim to recruit high-risk men who have sex with men, specifically Latino and/or Black/ African-American men. According to the CDC, Black/African American MSM accounted for the largest number of HIV diagnoses in 2016, followed by Latinos[58]. Additionally, HIV diagnoses increased among Latinos. Our research will help understand how to reach these high-risk populations. Our promotion strategy will employ culturally appropriate advertisements, including images and text. If difficulty is encountered in recruiting an adequate number of minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging strategies such as expanding to additional online sites belonging to one of the three platforms.

15.9 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. This study will not target prisoners and will not assess prisoner status. Certification from OHRP to enroll prisoners will not be obtained for this study.

15.10 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be stored electronically and checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

15.11 Records Retention and Requirements

Research records for all study participants (e.g., electronic data collection forms and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. Electronic study records, namely forms, databases, source documents will be stored on a secure computer within UCLA.

A password will be used to limit access and protect participant information. The Lead PI will know the password. No paper study records will be kept. The sponsor and Lead Investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of electronic research records.

15.12 Reporting to Sponsor

The site Principal Investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event reporting and Serious Adverse Event reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

15.13 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the Northeast Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the sites' Institutional Review Board may inspect electronic research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

15.14 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records, if applicable) for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all electronic data collection forms, workbooks, monitoring logs and appointment schedules, sponsor-investigator correspondence, signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence and approved consent form. As part of participating in a NIDA-sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

15.15 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/ exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/ approved by the Lead Node with overall approval by the UCLA IRB. All protocol deviations will be monitored at the site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

The Lead Investigator must be contacted immediately if an unqualified or ineligible participant is recruited into the study. Protocol deviations or violations will be reported to the Lead Node and the Clinical Coordinating Center, who will both work directly with the site to take corrective actions. In the unlikely event a protocol deviation compromises the integrity of the trial, the Lead Node will notify the Sponsor.

Additionally, the study site is responsible for reviewing the IRB of record’s definition of a protocol deviation or violation and understanding which events need to be reported. The study site must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

15.16 Safety Monitoring

15.16.1 Data Safety Monitoring Board (DSMB)

As this is a minimal risk study and no safety analysis will be performed (and no events are anticipated), an independent CTN DSMB will not be convened for this study. Instead, an independent Protocol Review Board (PRB) will approve the protocol prior to implementation and is responsible for conducting consultations on the study as needed. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, or inadequate trial performance (e.g., poor recruitment), or any Corrective Preventative Action (CAPA), if needed.

In the unlikely event that a safety issue arises, the AE will be reported to the study IRB at UCLA, following that institution's reporting policies. Other study monitoring will be performed by the local QA and/or CCC monitors as described in Section 15.7.

15.16.2 Adverse Events (AEs)

It is unlikely that HIV status will result in a participant intending harm upon themselves or others; however, should this occur, the medical monitor at the UCLA IRB will evaluate whether any such event was related to the study and the lead team will immediately notify the LN and Sponsor. Because this is a minimal risk study with no behavioral intervention or clinical contact, no assessments will specifically inquire about suicidality/homicidality. The only way study staff will learn of this is if a participant calls the study-specific phone number provided to them at the time of consent and tells a study team member of their thoughts/intentions. Standard Operating Procedures for this scenario will be developed alongside/as part of the Manual of Operating Procedures for this study and will follow all policies and procedures of the UCLA IRB. These data will be submitted to the UCLA IRB within 10 working days of PI awareness, as per that institution's policy.

Adverse Events

The only study activity associated with risk is the participant learning he is HIV positive. Only adverse events directly related to learning of HIV status will be captured and reported to the UCLA IRB.

Serious Adverse Events

Serious adverse events directly related to learning of HIV status will be captured, however, based on the study team's experience this is unlikely.

In the event that a Serious Adverse Event (SAE) becomes known, the Lead Investigator will immediately review the participant's electronic file and an event report (this process will be developed as a SOP alongside/as part of the study MOP). These reviews will include assessment of the possible relatedness of the event to learning HIV positive status or other study procedures. The Lead Investigator will also determine if it is necessary to exclude, refer, or withdraw participants as required. In addition, the UCLA IRB has dedicated staff who will act as the Medical Monitor to the protocol to independently review the safety data and provide PIs a Safety Letter when necessary. The Lead Node will determine which safety events require expedited reporting to NIDA and regulatory authorities. This will include events that are serious, related and unexpected, though we anticipate these will be rare. The study staff will be trained to monitor for and report Adverse Events and Serious Adverse Events.

UCLA has established practices for managing psychiatric emergencies, and study staff will utilize these

procedures. Participants will be provided with the number for the Substance Abuse and Mental Health Services Administration (SAMHSA) 24/7 National Helpline at baseline and they will be encouraged to call if they feel depressed or have suicidal thoughts after getting their result. Additionally, we will provide the contact information of local AHF test sites, which have trained staff and clinicians, and recommend that participants visit these sites for testing and necessary services.

15.16.3 Medical Monitor

Detailed Safety Monitoring will not occur via the CCC or Lead Node, due to the minimal risk nature of this study. The UCLA IRB will be responsible for reviewing all adverse events and serious adverse events reported, should there be any. All SAEs will be reviewed as close to the time they are reported as possible. Any AEs that occur will be reviewed on a weekly basis as part of the study team meeting to observe trends or unusual events. A SOP will be developed to identify notification paths to the LN, sponsor, and all study team members. All AEs will be reported to the UCLA IRB.

The Lead Node will in turn report events to the sponsor and regulatory authorities if the event meets the definition of an expedited event.

16.0 DATA MANAGEMENT

16.1 Design and Development

This protocol will involve a unique data collection and transfer plan. Experts in the specific analyses of these data, all of whom are collaborators on this protocol, reside at the University of California, Los Angeles (Lead Investigator Klausner) or Dartmouth College (Lead Node Investigator Marsch). As data collection occurs entirely online, the process for collection will be developed by the UCLA team. Data collection modalities vary in this study; participants' responses will be entered directly into the database, while the performance metrics of the advertisement sites will be received independently in the form of weekly reports generated by each advertisement service. Additionally, OraSure (the manufacturer of OraQuick®) will independently provide reports on claimed vouchers for HIV home self-test kits on an approximately weekly basis. The flow of these different data will be depicted in the MOP. By the end of the study, all data collected will reside primarily at UCLA for storage. Dartmouth College will receive data based on the agreement put in place between the two institutions. The UCLA team and Lead Node will comply with any and all data management and sharing requirements of the sponsor. The remainder of this section provides an overview of the data management plan associated with this protocol.

16.2 Site Responsibilities

The data management responsibilities for the recruitment site, University of California, Los Angeles (UCLA), will be developed with input from the members of the protocol development team, including individuals from the Lead Node, UCLA, and the DSC.

The following provides a summary of each center's role in data collection and management:

University of California, Los Angeles (UCLA)

It is the responsibility of UCLA investigators to ensure processes are in place for the collection and management of all data from the study. The UCLA team will develop the data collection tool for demographic and related risk surveys and will be responsible for participant recruitment, baseline and follow-up data collection, and data quality/management.

Northeast Node, National Drug Abuse Treatment Clinical Trials Network

The Northeast Node will be responsible for all study quality assurance monitoring. The Northeast Node (Dartmouth College) will receive data based on the agreement put in place between the two institutions. Once data collection is complete and the database is closed, the dataset will be transferred between UCLA and the Northeast Node for data analyses according to the agreement put in place between the two institutions.

ETR

ETR will be responsible for implementing the advertisement strategy and development of the study website, which will include details such as information on availability and contact information for testing and PrEP services. Data on advertising performance metrics (e.g., cost per click and conversion rate tracking and comparison) across the various advertising sites and conditions will be reported to the project coordinator on an approximately weekly basis. The ETR team will not collect participant information and will not have any role in data management or analysis.

16.3 Data Collection

The data collection process varies and is dependent on the type of data collected. Data will be stored on secure and encrypted servers. Data may be backed up to secondary secure and encrypted servers or hard drives.

Advertising Performance Metrics

Advertising performance metrics will be collected via secure website. As participants navigate to either social media sites, dating apps or informational sites, data on the number of clicks on targeted HIV testing and PrEP advertisements and health promotion seeking behavior (e.g., number of ordered HIV test kits and number of participants linked to PrEP services) will be tracked.

Study Assessment Data

All study assessment data (e.g., demographic survey, risk survey, TAPS Tool, TTM) will be collected via an online self-report survey housed on the UCLA Health Qualtrics page. Primary data storage will be on secure and encrypted servers at UCLA.

Photographs

All photographs received of participants' HIV test results will be taken by study participants and uploaded to the Qualtrics website during the follow-up assessments. The study team will convert the test result shown in the image to text and delete the image itself. HIV test results will be entered into a secure database by UCLA researchers and stored at UCLA on secure servers. Data will be shared between UCLA and Dartmouth according to the agreement put in place between the two institutions.

16.4 Data Acquisition and Entry

All study data will be captured electronically from participants via the Qualtrics survey site managed by the study team at UCLA. Advertising performance information will be recorded automatically by the websites (ETR) and reported on an approximately bi-weekly basis.

16.5 Data Editing

Due to the nature of the study (self-reported, voluntary responses), quality checks and controls to validate participant-submitted responses are not feasible. To ensure consistency and high quality data, reminders are planned to encourage participants to complete each assessment (see 8.3.3), but given the time limited nature of the study (30-day waves and time windows for completion of each follow-up), no further plan is in place to address questions that participants do not answer.

The UCLA study team will perform an approximate monthly check on the logs used for managing the study to ensure consistency and quality of the study activities and data collected during enrollment and follow up. This may include the Master enrollment log, the validation log, the Communications Log, Master inventory Log, as well as review for cases who report a preliminary positive HIV result.

16.6 Data Transfer/Lock

Only authorized individuals shall have access to study data. Data will be transferred among study collaborators for analyses and data quality monitoring. All data will be collected and stored at UCLA. Dartmouth College will receive data based on the agreement put in place between the two institutions. At the conclusion of data collection for the study, the Lead Node will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset

will be transferred to UCLA for storage and archive and to Dartmouth for analysis according to the data transfer agreement between the two institutions. The dataset will be transferred to the DSC for storage at the end of the study.

16.7 Data Training

The training plan for site staff includes provisions for training on assessments and data management procedures, and the use of the electronic data capture program (Qualtrics). Our team has used Qualtrics in a previous project and is already familiar with basic functions of the software.

16.8 Data Quality Assurance

To address the issue of data quality, data from active study measures will be monitored by the Lead Node and will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

17.0 PUBLIC ACCESS AND DATA SHARING PLAN

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) and (for HEAL-funded studies) the HEAL Public Access and Data Sharing Policy (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/research/heal-public-access-data-sharing-policy). Investigators will also register and report results of the trial in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration (https://grants.nih.gov/policy/clinical-trials/reporting/ understanding/nih-policy.htm).

Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. For more details on data sharing please visit https://datashare.nida.nih.gov/.

The primary outcome(s) publication will be included along with study underlying primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

18.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 5.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

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20.0 APPENDIX A: ADVERSE EVENT REPORTING AND PROCEDURES

Each participating site's Principal Investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

Definition of Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study medication/intervention related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status, ECGs, lab results, x-rays, physical examinations, etc., that is considered clinically significant by the study medical clinician are considered AEs. **For the purpose of this study, only AEs directly related to learning of HIV positive status will be captured.**

An **adverse event** is considered "**serious**" (i.e., a serious adverse event,) if, in the view of either the study medical clinician or sponsor, it:

1) Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study [medication/intervention], must be reported.
2) Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.
3) Requires inpatient hospitalization or prolongation of existing hospitalization.
4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) Is an important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed at the specificity or severity that has been observed. If neither is available, then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy

This study will recruit only men.

Site's Role in Eliciting and Reporting Adverse Events

This is a minimal risk study and the possibility of adverse events is low. The study team will not specifically elicit AEs from participants over the course of the study. However, if a participant spontaneously reports an adverse event at either a follow-up or when contacting the research team directly by phone or email, the study team will follow UCLA IRB's reporting policies and procedures. Standard reporting, within 10 days of the site becoming aware of the event is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is

required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to the IRB of record, per the IRB or record's guidelines.

The study team will enter reportable AEs and SAEs into a database (e.g., an online database and/ or a protected spreadsheet) at UCLA. Additional information may need to be gathered to evaluate SAEs, and this information will also be captured in the database. Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event:

Grade 1	**Mild**	Transient or mild discomfort (typically <48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	**Moderate**	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.

Guidelines for Determining Causality

Qualified study personnel will use the following question when assessing causality of an adverse event to study medication/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study intervention caused the event?

Site's Role in Monitoring Adverse Events

Local quality assurance monitors will review study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

Lead Node's Role in Safety Management Procedures of AEs/SAEs

A safety monitor is not required for this study.

Participant Withdrawal

Appropriately qualified study staff at UCLA must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be withdrawn from further study intervention. The qualified study staff member should consult with the site Principal Investigator, the lead investigator and/or UCLA IRB staff as needed. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be given recommendations for medical care and/or referrals to treatment, as necessary.

21.0 APPENDIX B: DATA AND SAFETY MONITORING PLAN

21.1 Brief Study Overview

The main goal of the study is to compare the effectiveness of HIV self-testing promotion in social media sites versus informational sites versus dating sites. Our team will place culturally appropriate online advertisements to the three types of websites. We will recruit approximately 400 MSM using an online survey. Upon enrollment, participants will fill out a Baseline electronic survey and upon completion of the survey participants receive instructions on how to order the free Home HIV test kit and receive information on HIV prevention and PrEP. The study team will follow up with the participants on two timepoints, 14-days and 60-days after enrolment. During the follow-up(s) participants will be asked about their test kit result, if they visited a health provider to start PrEP or reasons for not starting PrEP. Secondary outcomes will explore the effectiveness of promotion in the study sites in the PrEP uptake, the impact of drug use, stigma, and stage of change to HIV self-testing uptake and PrEP uptake.

21.2 Oversight of Clinical Responsibilities

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

All adverse events (AEs) occurring during the course of the clinical trial and meeting the protocol-defined reporting criteria will be collected, documented, and reported by the study team according to the Protocol.

The occurrence of AEs and serious adverse events (SAEs) will be assessed on an ongoing basis. Serious adverse events will be followed until resolved or considered stable. Since this is a minimal-risk study, no unanticipated events are expected.

Reportable AEs are required to be reported to the Lead Team (including the Lead Node, study Sponsor, and CCC) within 10 days of the site staff becoming aware of the event. Reportable SAEs (including death and life-threatening events) are required to be reported to the Lead Team within 24 hours of site's knowledge of the event).

B. CCC (or Lead Node) Safety Monitor/Medical Monitor

Since this is a minimal risk study, neither a CCC (nor Lead Node) Safety Monitor or Medical Monitor will be appointed for this study. Any AE/SAEs will be reported to the UCLA IRB. If any AE/SAEs are reported to the UCLA IRB, the Lead Team (including UCLA Site Staff, Lead Node Staff, the Lead Investigators, CCC, DSC and NIDA CCTN) will be notified on an Ops Call and this information will be included in the cumulative Weekly report that is provided to the Lead Team.

C. Protocol Review Board (PRB)

Due to the minimal risk evaluation of the study, there will not be a NIDA CTN DSMB affiliated with this trial. Instead, an independent CTN PRB is responsible for conducting consultations on the study as needed. The PRB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment) or any Corrective Preventative Action (CAPA), if needed.

Following each PRB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on PRB recommendations, in writing to the study Lead Investigator.

Any safety events identified will be monitored by the UCLA IRB.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site(s) will be conducted on a regular basis using a combination of NIDA CCTN CCC monitors (if applicable) and the Lead Node QA Monitors. Investigators will host periodic visits for the NIDA CCTN CCC monitors and/or Lead Node QA Monitors. The purpose of these visits is to assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as to document the integrity of the trial progress. The investigative site will provide direct access to all trial related locations (e.g., pharmacy, research office), source data/documentation, and reports for the purpose of monitoring and auditing by the CCC and Lead Node monitors, as well as inspection by local and regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant informed consent forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

Site Visit Reports will be prepared by the NIDA CCC monitors following each site visit. These reports will be sent to the site Principal Investigator, the study Lead Investigator and NIDA CCTN.

Lead Node QA Monitors will prepare site visit reports, which are sent to those entities required of them by the Lead Investigative team, generally including the Lead Investigator, site Principal Investigator, Node PI and a CCC representative, usually the Protocol Specialist for the study.

E. Management of Risks to Participants

Confidentiality
Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs (Case Report Forms), and secure storage of any documents or electronic files that have participant identifiers, as well as secure computing procedures for entering and transferring electronic data. The logs linking the study codes with the study participant will be kept stored on the secure and encrypted UCLA Qualtrics server. No identifying information will be disclosed in reports, publications or presentations.

Participant Protection
Participants who report a preliminary positive HIV test result will be referred to local clinics to receive confirmatory testing and receive treatment for HIV, if needed.

Pregnancy
The study will recruit only men. No women will be included in the study.

Study Specific Risks
The primary potential risks to participants due to study participation are psychological and social in nature. Participants could experience psychological distress, such as anxiety when discussing issues related to personal experiences (e.g., substance use, sexual history). However, we do not expect any serious events to occur based on our experience across multiple previous studies[6][7][28][29]. Participants may experience some stress related to the knowledge of HIV status; however, the likely harmful consequences of learning one's HIV status are low. Participation in this study may cause social harm (e.g., discrimination, rumors) if the involvement of the participant becomes known to others. There is also a potential risk of loss of confidentiality.

21.3 Data Management Procedures

Data will be managed by the site staff at UCLA. A web-based distributed data entry model will be implemented. This electronic data capture system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld. We will use UCLA Health Qualtrics Survey Software to collect participant data. This is a HIPAA and FERPA- compliant secure online survey platform.

The data management responsibilities for the recruitment site, University of California, Los Angeles (UCLA), will be developed with input from the members of the protocol development team, including individuals from the Lead Node, UCLA, and the DSC.

The following provides a summary of each center's role in data collection and management:

University of California, Los Angeles (UCLA)
It is the responsibility of UCLA investigators to ensure processes are in place for the collection and management of all data from the study. The UCLA team will develop the data collection tool for demographic and related risk surveys and will be responsible for participant recruitment, baseline and follow-up data collection, and data quality/management.

Northeast Node, National Drug Abuse Treatment Clinical Trials Network
The Northeast Node will be responsible for all study quality assurance monitoring. The Northeast Node (Dartmouth College) will receive data based on the agreement put in place between the two institutions. Once data collection is complete and the database is closed, the dataset will be transferred between UCLA and the Northeast Node for data analyses according to the agreement put in place between the two institutions.

ETR
ETR will be responsible for implementing the advertisement strategy and development of the study website, which will include details such as information on availability and contact information for testing and PrEP services. Data on advertising performance metrics (e.g., cost per click and conversion rate tracking and comparison) across the various advertising sites and conditions will be reported to the project coordinator on an approximately weekly basis. The ETR team will not collect participant information and will not have any role in data management or analysis.

21.4 Data Collection and Entry

The data collection process varies and is dependent on the type of data collected. Advertising performance information will be recorded automatically by the website and reported on an approximately weekly basis. All study assessment data (e.g., demographic survey, risk survey, TAPS Tool, TTM) will be collected via an online self-report survey housed on the UCLA Health Qualtrics page. All photographs received of participants' HIV test results will be taken by study participants and uploaded to the Qualtrics website during the follow-up assessments.

The Principal Investigator at the site is responsible for maintaining accurate, complete and up-to- date research records. In addition, the site Principal Investigator is responsible for ensuring the timely completion of data collection forms for each research participant.

21.5 Data Monitoring, Cleaning and Editing

Due to the nature of the study (self-reported, voluntary responses), quality checks and controls to validate participant-submitted responses are not feasible. To ensure consistency and high quality data, reminders are planned to encourage participants to complete each assessment (see 8.3.3), but given

the time limited nature of the study (30-day waves and time windows for completion of each follow-up), no further plan is in place to address questions that participants do not answer.

The UCLA study team will perform an approximate monthly check on the logs used for managing the study to ensure consistency and quality of the study activities and data collected during enrollment and follow up. This may include the Master enrollment log, the validation log, the Communications Log, Master inventory Log, as well as review for cases who report a preliminary positive HIV result.

De-identified data reports from Qualtrics and OraSure will be sent securely (e.g., with encryption and password protection) by UCLA site staff to the Lead Node for backup on a password- protected hard drive at least monthly.

If issues with data security/availability are identified (e.g., potential corruption, data loss, or hack), the issue will be reported to the Lead Team (including the Lead Node, study Sponsor, and CCC) within 10 days of the site staff becoming aware. Appropriate actions will be determined by the Lead Team as appropriate to the specific issue encountered and in collaboration with other parties (e.g., Qualtrics, Dartmouth/UCLA Information Technology/Support, or IRB) as relevant.

As described above, the CCC and/or Lead Node QA Monitor will conduct regular remote or in- person visits to site, during which audits of the study data will be performed. Study data reports will be provided to the study team on an approximate weekly basis. Advertising performance information will be recorded automatically by the websites and reported on an approximate bi- weekly basis by ETR via a cumulative advertising report. In addition, the study data report will contain study information downloaded from Qualtrics by the UCLA site staff, such as recruitment, enrollment, participant follow-up progress and participant study completion. The report will also include self-test kit order numbers as provided to UCLA site staff by OraSure. This report will be generated approximately weekly and will be provided to the Lead Team (including UCLA Site Staff, Lead Node Staff, the Lead Investigators, CCC, DSC and NIDA CCTN), to monitor the site progress.

21.6 Database Lock and Transfer

Only authorized individuals shall have access to study data. Data will be transferred among study collaborators for analyses and data quality monitoring. All data will be collected and stored at UCLA. Dartmouth College will receive data based on the agreement put in place between the two institutions. At the conclusion of data collection for the study, the study team at UCLA will perform final data cleaning activities and will “lock” the study database from further modification. The final analysis dataset will be transferred to the Lead Investigator or designee. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated parties for posting on the NIDA Data Share website, as well as storage and archiving. The dataset will be transferred to the DSC for storage at the end of the study.

Reference: http://grants.nih.gov/grants/guide/notice-files/not98-084.html

22.0 APPENDIX C: CONFIDENCE INTERVALS

DEMONSTRATION THAT THE INTERVAL BETWEEN THE 10TH PERCENTILE OF THE LOWER CONFIDENCE LIMIT AND THE 90TH PERCENTILE OF THE UPPER CONFIDENCE LIMIT COMPLETELY CONTAINS MORE THAN 80% OF THE CONFIDENCE INTERVALS.

Let us indicate a particular lower boundary by l, and the 10th percentile of lower boundaries, with L, and, neglecting the possibility of equality, let us write lL if the particular lower boundary is below L, and Ll if the particular boundary is above L. Similarly, we can use u and U for a particular upper boundary and the 90th percentile of upper boundaries, with uU and Uu indicating whether the particular upper boundary is below or above the 90th percentile of upper boundaries. Then, because L is less than U and u is less than U, there are only 6 possibilities for the joint arrangements of lower and upper boundaries and percentiles:

A: luLU
B: lLuU
C: LluU
D: lLUu
E: LlUu
F: LUlu
Where P(A) + P(B) + P(C) + P(D) + P(E) + P(F) = 1. Because of the definitions of L and U, we must have P(A) + P(B) + P(D) = 0.1 and P(D) + P(E) + P(F) = 0.1. We seek the probability that a confidence interval will lie entirely in (L, U), namely P(C). We have:

$$
\begin{aligned}
P(C) &= 1 - [P(A) + P(B) + P(D) + P(E) + P(F)] \\
&\geq 1 - [P(A) + P(B) + 2P(D) + P(E) + P(F)] \\
&= 1 - [0.1 + 0.1] = 0.8
\end{aligned}
$$

So, the probability that the confidence interval is entirely enclosed by (L, U) is at least 0.8.