The iTest Study: A single-center, randomized, open-label parallel-group superiority study to compare the effects of access to HIV self-testing at no cost versus standard HIV testing alone on HIV testing frequency among men who have sex with men at high risk of HIV acquisition

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TRIAL REGISTRATION DATA

Primary registry and trial identifying number	ClinicalTrials.gov NCT01161446
Date of registration in primary registry	July 9, 2010
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Source(s) of monetary or material support	U.S. National Institute of Mental Health; University of Washington Center for AIDS Research; Public Health – Seattle & King County HIV/STD Program
Primary sponsor	U.S. National Institute of Mental Health
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Public title	Home Self-Testing for HIV to Increase HIV Testing Frequency in Men Who Have Sex With Men (The iTest Study)
Scientific title	The iTest Study: A single-center, randomized, open-label parallel-group superiority study to compare the effect of access to free HIV self-testing versus standard HIV testing alone on HIV testing frequency among men who have sex with men at high risk of HIV acquisition
Country of recruitment	U.S.
Health condition/problem studied	Human immunodeficiency virus
Interventions	Experimental: HIV self-testing Participants in this arm will be given access to HIV self-testing kits with the OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test for use with oral fluids at no cost. They will be trained to use this device to test themselves

	for HIV and be able to request up to one self-testing kit per month throughout follow-up.
	No intervention: Standard HIV testing
Key inclusion criteria	Self-identified or biological man
	Age 18 years or older
	Reports sex with men in year prior to enrollment
	Documented HIV-negative within 30 days prior to enrollment
	At high risk for HIV acquisition per 2010 Public Health – Seattle & King County guidelines (http://www.kingcounty.gov/healthservices/health/communicable/hiv/providers/msmstd.aspx)
	Plans to live in study area for next 15 months
	Accepts healthy human volunteers
Key exclusion criteria	Unable to safely and confidentially receive or store a home testing kit
Date of first enrollment	September 2010
Sample size	230
Recruitment status	Complete
Primary outcome	HIV testing frequency (time frame: 15 months; not designated as safety issue)
Secondary outcomes	Self-reported sexual risk behaviors (time frame: 6 to 9 months and 12 to 15 months; not designated as safety issue). Includes number of male condomless anal sex partners and condomless anal sex with male partners of unknown or discordant HIV status.
	Bacterial sexually transmitted infections (STI) (time frame: assessed at 15 months; not designated as safety issue). Includes early syphilis, gonorrhea, and chlamydial infection.

PROTOCOL AMENDMENTS

Amendment 1: After study staff learned that a participant had shared a study self-testing kit with a sex partner and the sex partner received a reactive result, the University of Washington Human Subjects Division requested revisions to study procedures, informed consent procedures, and HIV self-test instructions to minimize the possibility that tests would be shared in the future. The informed consent process has been revised to inform participants that they will be removed from the study if staff learn they have shared a study test kit. The test kit instructions have been revised to address the importance of keeping the test kits secure and not making them available to others. A letter will be sent out to inform participants already enrolled in the trial of these changes in procedures. *Amended May 2, 2011.*

Amendment 2: 'Planning to live in the study area for the next 15 months' is an eligibility criterion for participation, and study staff ask participants to inform them prior to leaving the Seattle area if they do end up relocating so that an in-person Off-Study visit can be scheduled.

However, some participants move to other states during follow-up without informing study staff and, when staff contact them to schedule the Off-Study visit, express interest in completing study procedures from outside the Seattle area. In order to obtain follow-up information from these participants, the protocol was revised to allow these visits to be conducted remotely. As with in-person visits, participants will complete the Off-Study survey and event history calendar, will be asked to consent to release the results of any clinic-based HIV/STI testing to study staff, and if they would like to be informed of study results. Participants will be asked to seek HIV/STI testing at a clinic as part of the remote end-of-study visit and share documentation of these results with study staff. *Amended July 12, 2012.*

Amendment 3: The data and safety monitoring plan was revised to include a single interim analysis by an independent data and safety monitoring board (DSMB) using O'Brien-Fleming stopping rules. Although an interim analysis was not originally planned, the U.S. Food and Drug Administration approved the OraQuick In-Home HIV Test in July 2012, and this test became available in pharmacies and online in October 2012. The test includes a nearly identical test device to the OraQuick ADVANCE Rapid HIV-1/2 Antibody Test for professional use included in the study self-testing kits used in this trial. With an HIV self-test available for consumer purchase and public health programs interested in utilizing these tests in prevention and testing programs, there was an urgent need for data regarding the impact of self-testing on HIV testing frequency and sexual risk behaviors among high risk populations and to conduct an interim analysis to determine whether results from our study can help inform these discussions in a timely manner. Therefore, with the approval of the UW Human Subjects Division and Program Officer at the National Institute of Mental Health, an independent DSMB was constituted to conduct an interim analysis at the mid-point of the study to determine whether to continue the study as is; stop the study early for efficacy, futility, or safety; or continue the study with modified procedures. To address potential concerns regarding contamination of the intervention, the statistical analysis plan has been revised to include a comparison of the effects of access to HIV self-testing on testing frequency prior to versus after commercial availability of the OraQuick In-Home HIV Test in October 2012. *Amended February 22, 2013.*

Amendment 4: The total number of study participants to enroll was revised from 246 to 230. There were budgetary concerns about the additional time necessary to complete enrollment, and greater than expected retention at 15 months ensured that enough participants would complete follow-up to maintain the level of statistical power described in the original protocol (n=197). *Amended September 30, 2013.*

Amendment 5: The statistical procedures for assessing the non-inferiority of self-testing compared with standard testing with respect to the number of male condomless anal sex partners was revised. The original plan to conduct generalized estimating equations (GEE) linear regression on the $\log_{10}$-transformed number of partners could not be used because some participants reported zero partners, and the analysis would therefore have been sensitive to the assumptions made regarding zeros prior to transformation. Instead, GEE Poisson regression with robust variance will be utilized to estimate the same outcome, the 95% confidence interval of the fold-difference in the number of partners between the two study arms. *Amended February 10, 2015.*

FUNDING
This trial is supported by the U.S. National Institute of Mental Health (grant number: R01 MH086360). The funding agency had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

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JDS conceived of the study. JDS, DAK, MRG, CF, and JPH contributed to the study design, and JDS and DAK will implement the study. JDS is the grant holder. JPH will provide statistical and clinical trial expertise. DAK will conduct the primary statistical analysis. All authors will contribute to refinement of the study protocol and will approve the final manuscript.

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1. INTRODUCTION

1.1 Background and Prior Research

Increasing HIV testing coverage and frequency has the potential to significantly impact HIV transmission because many individuals newly diagnosed with HIV infection will alter their behaviors to reduce the risk of transmission to others and timely treatment to reduce HIV RNA levels can reduce the infectiousness of HIV-infected individuals. In the U.S., men who have sex with men (MSM) still represent the group with the greatest risk for HIV acquisition despite a high penetrance of testing, in part because their frequent exposures and infrequent testing can result in long intervals between HIV acquisition and diagnosis. Efforts to prevent HIV transmission among MSM must therefore increase the frequency of HIV testing and decrease the time that infected individuals are unaware of their status and their potential for transmission. HIV self-testing may increase the frequency of HIV testing by reducing barriers to testing such as the need to attend a clinic, concerns about confidentiality, and discomfort with venipuncture, as well as by increasing individuals' control over the test. However, there are concerns that it may also have negative consequences, including decreased access to risk reduction counseling and STI screening, an increase in false negative test results due to the longer window period of available rapid tests, misinterpretation of test results, missed opportunities to link HIV-positive persons into care or to perform partner services, and reduced accuracy of surveillance. To date, no studies have evaluated the effect of HIV self-testing on testing frequency or risk of HIV acquisition in an at-risk population. The iTest Study will randomize HIV-negative MSM at high risk for HIV acquisition to have access to HIV self-testing using the OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test (OraQuick) on oral fluids at no cost or to standard HIV testing for 15 months to determine whether the availability of self-testing will increase HIV testing frequency without negatively impacting their risk for HIV acquisition.

1.2 Rationale

The intervention, access to HIV self-testing with OraQuick at no cost over a period of 15 months with tests available upon request by mail or in-person pick up from a clinic, was designed to serve as a potential model for HIV testing programs to increase testing among MSM using self-tests. In the absence of an U.S. Food and Drug Administration (FDA)-approved self-test (at the time of study initiation), a study self-testing kit including the professional use OraQuick test, instructions, counseling materials, and access to a 24-hour contact was developed to closely mirror the test under consideration by the FDA, a test based on OraQuick on oral fluid with supporting materials discussed at meetings of the Blood Products Advisory Committee. Standard of care, i.e. HIV testing as usual, was selected as the comparator to focus the comparison on the addition of self-testing on oral fluid at no cost as an HIV testing option on testing frequency and risk of HIV acquisition.

2. STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

The primary objective of this study is to **compare HIV testing frequency among high risk MSM randomized to have access to HIV self-testing at no cost versus those randomized to standard HIV testing** (test of superiority). Men will report the number of HIV tests they

received during 15 months of follow-up using a self-administered computer-based survey at the Off-Study visit. We hypothesize that access to self-testing will increase testing frequency when compared to standard testing alone by providing an additional testing option that is convenient, anonymous, non-invasive, and controlled by the individual.

2.2 Secondary Objective

The secondary objective of this study is to determine whether HIV self-testing is non-inferior to standard HIV testing with respect to the following markers for risk of HIV acquisition:

1. Prevalence of bacterial sexually transmitted infections (STIs: chlamydial infection, gonorrhea, and early syphilis) at 15 months of follow-up,
2. Self-reported condomless anal intercourse (CAI) with male partners of unknown or discordant HIV status from 6 to 9 and 12 to 15 months of follow-up, and
3. Self-reported number of male CAI partners from 6 to 9 and 12 to 15 months of follow-up.

STI screening will be performed at the Off-Study visit. Men will report sexual behaviors during the last 3 months using an online survey at month 9 of follow-up and using a self-administered computer-based survey at the Off-Study visit at month 15. We hypothesize that men randomized to self-testing will demonstrate equivalent or less risk of HIV acquisition when compared with men randomized to standard testing (i.e., self-testing is non-inferior to standard testing), thereby reducing concerns regarding the absence of risk reduction counseling as part of self-testing. Standard risk reduction counseling has not been shown to reduce risk behaviors among HIV-negative men, and the Centers for Disease Control and Prevention's (CDC) HIV testing guidelines advocate the decoupling of risk reduction counseling and HIV testing.

2.3 Trial Design

The iTest Study is designed as a randomized, controlled, open label single-center superiority trial with two parallel groups and a primary endpoint of number of HIV tests during 15 months of follow-up. Randomization will be performed with a 1:1 allocation using blocks of random size.

The study visit schedule and procedures are described in detail in the Methods section below. Briefly, participants will complete a screening visit prior to enrollment to determine eligibility, including ensuring documentation of a negative HIV test within 1 month of enrollment. At the enrollment visit, participants will provide informed consent, receive allocation to the intervention or control arm, receive HIV/STI screening, and complete a self-administered survey. During follow-up, participants will test for HIV infection at the time(s) and location(s) of their choice (including study self-tests in intervention arm), receive testing reminders if requested, and complete quarterly contact information surveys online (the 9-month survey includes two behavior questions addressing markers of HIV risk). At either 15 months or after a confirmed positive HIV test, participants will complete a final study visit including HIV/STI screening and a self-administered survey addressing testing frequency and markers of HIV risk.

3. METHODS

3.1 Study setting

The Screening, On-Study, and Off-Study visits will be conducted at the PHSKC STD Clinic, which performs the majority of the clinical activities of the PHSKC HIV/STD Program. The PHSKC Laboratory will perform HIV enzyme immunoassays (EIA) and Western Blots as well as all STI screening. The University of Washington Clinical Retrovirology Laboratory will conduct pooled HIV nucleic acid amplification testing (NAAT).

3.2 Eligibility criteria

Individuals who meet the following criteria will be eligible to participate in the trial:

- Self-identified or biological male
- Age 18 years or older
- Reports sex with men in year prior to enrollment
- Documented HIV-negative test within 30 days prior to enrollment
- At high risk for HIV acquisition per PHSKC guidelines, i.e. reports at least one of the following in the prior year: CAI with partners of discordant or unknown HIV status, a bacterial STI (includes syphilis, gonorrhea, and chlamydial infection), methamphetamine or popper use, or ≥10 male oral or anal sex partners (2010 guidelines available at http://www.kingcounty.gov/healthservices/health/communicable/hiv/providers/msmstd.aspx)
- Able to provide a stable home or mailing address
- Planning to live in the Seattle area for the next 15 months

Only high risk MSM will be enrolled so that recommendations for quarterly HIV testing are uniform among study participants and consistent with PHSKC guidelines.

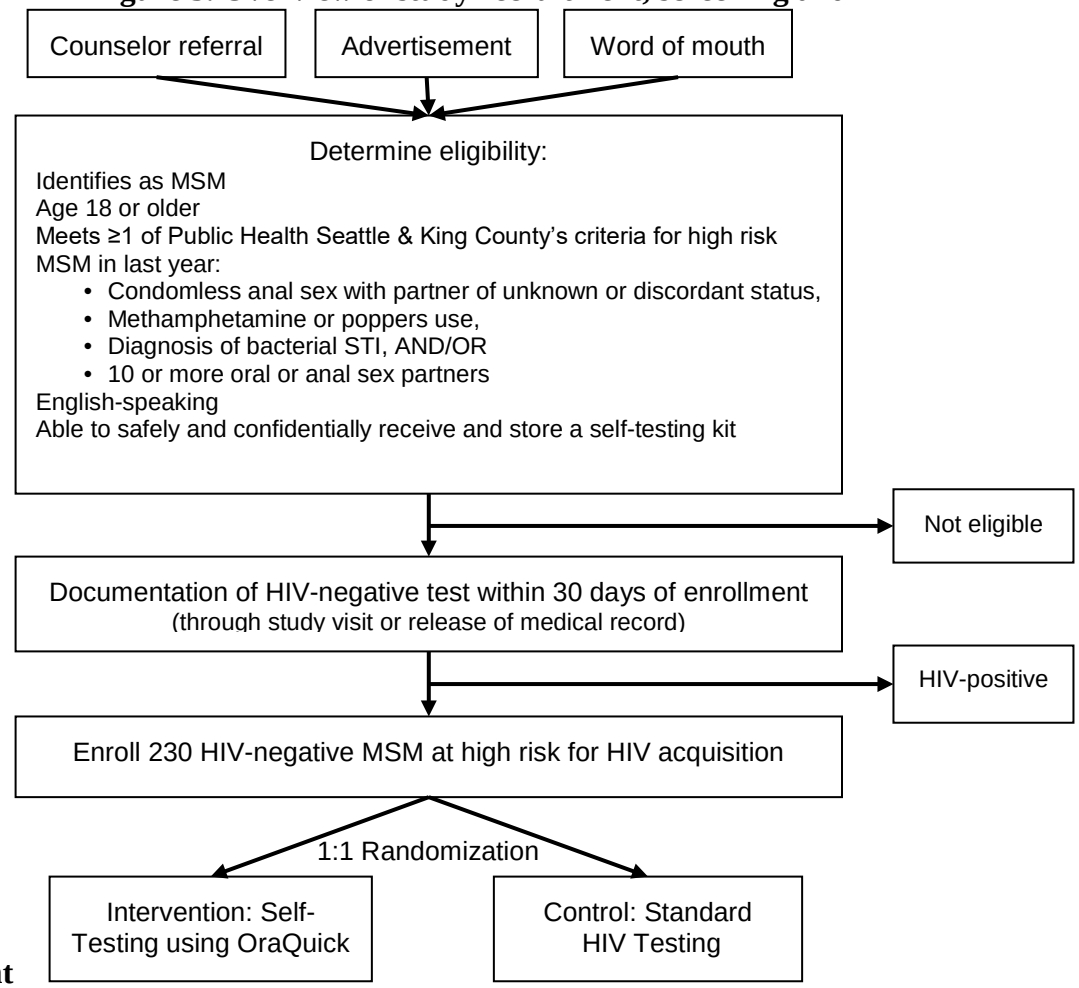
3.3 Exclusion critiera

MSM under the age of 18 or who are unable to provide a stable home or mailing address will be excluded to minimize difficulties in storing, receiving, and utilizing the self-testing kits. MSM participating in HIV vaccine trials or NEXT-PrEP (HPTN 069/ACTG 5305) will be excluded because these studies include protocol-specified HIV testing at regular intervals.

3.4 Study procedures and interventions

Figure 3 provides an overview of study recruitment, screening, and enrollment, and Table 3 describes the schedule of study evaluations. At the Screening visit, the study coordinator will discuss study participation with eligible MSM. Potential participants who do not have documentation of a negative HIV test within the prior month will have blood drawn for HIV testing by EIA and NAAT. HIV antibody-negative MSM will be eligible for study enrollment; participants who subsequently test HIV NAAT-positive will be taken off study.

Figure 3. Overview of study recruitment, screening and enrollment



At the On-Study visit, participants will sign informed consent for study participation and complete a computer-based, self-administered questionnaire that will ask questions regarding sexual behavior, substance use, and attitudes and beliefs regarding HIV infection and HIV testing. Participants will be screened for STIs including syphilis and rectal, urethral, and pharyngeal gonorrhea and chlamydial infection as per standard of care at the PHSKC STD Clinic. The OraQuick oral fluid rapid HIV test will be performed and blood will be drawn for HIV EIA and NAAT testing. Contact information for the participant and at least one friend or family member will also be obtained for tracking purposes during follow-up. At this visit, participants will be randomized in a 1:1 fashion to one of two arms:

<u>Intervention Arm: HIV self-testing using OraQuick</u>
Participants randomized to the intervention arm will have in-depth training in the performance of OraQuick and will receive a test kit at the On-Study visit. Test kits will include written instructions, pre- and post-test counseling materials, a list of local HIV/AIDS and related resources, and condoms. Participants will be advised to test quarterly and given a calendar marked with testing dates. Participants randomized to Arm 1 will be offered the opportunity to collect finger stick blood samples to mail to the study coordinator for backup HIV antibody testing and HIV NAAT to be performed by the University of Washington Clinical Retrovirology

Laboratory. After HIV testing, participants will complete an online questionnaire to report the date and location of testing, reasons for testing, acceptability and ease of use of the self-test if it was used, and interval sexual history and substance use. The study coordinator will mail a new test kit to participants upon request, but not more than once a month. A 24-hour telephone contact will be available for procedural questions, technical support, and counseling. Participants who test HIV-positive by self-testing will call the 24-hour contact for post-test counseling and to schedule an appointment for confirmatory testing. As of April 15, 2011, participants will be instructed not to share the test kit with others and will be removed from the study if study staff learn prior to the Off-Study visit that they have shared a test kit.

Control arm: Standard HIV testing (No intervention)
Participants randomized to the control arm will be advised to have quarterly HIV testing through visits to PHSKC-funded testing sites or other sites where HIV NAAT is routinely performed. Participants will be given a calendar marked with testing dates. Participants will complete online questionnaires to report the date and location of HIV testing, reasons for testing, and interval sexual history and substance use.

Participants in both arms will be educated about acute HIV infection and instructed to seek attention at the PHSKC STD Clinic for possible seroconversion symptoms. All participants will be offered reminders for testing by letter, phone, or email per current PHSKC protocol. To minimize overall loss to follow-up and limit differential loss to follow-up between study arms during the study period, all participants will complete quarterly online surveys to maintain intermittent contact with the study coordinator. Participants will be asked only to provide updated contact information to minimize the potential impact on testing frequency, except at 9 months when this survey will include two questions to assess (1) CAI with male partners of unknown or discordant HIV status and (2) number of male CAI partners, both during the previous 3 months. If a participant reports testing positive on the online questionnaire and has not contacted the study coordinator, he will be contacted as soon as possible for post-test counseling and to schedule confirmatory testing, a PHSKC One on One program visit (early access services for HIV-positive persons, including clinical assessment and facilitation of linkage to care), or Off-Study visit as appropriate. Participants who acquire HIV during the study period will have an Off-Study visit and will be referred for HIV care. Participants who request to end their participation in the study will be offered an Off-Study visit at that time.

At the end of the 15-month study period, participants remaining on-study will be scheduled for an Off-Study visit. At the Off-Study visit, participants will complete a computer-based, self-administered questionnaire that addresses HIV risk behaviors, STIs, and testing for HIV and STIs; blood will be drawn for HIV testing; and participants will be screened again for STIs. Participants will be asked to provide consent to release results of all non-protocol specified HIV/STI testing that occurred during the study period. Subjects will receive $20 for the On-Study visit, $10 for online surveys, and $40 for completion of the Off-Study visit.

3.5 Outcomes
Primary objective: The number of HIV tests received by participants during the 15 months of follow-up will be assessed by asking participants how many times they were tested for HIV during the previous 15 months as part of the self-administered computer-based questionnaire at

the Off-Study visit. Participants will complete an event history calendar prior to the questionnaire in order to assist with recall[40].

Secondary objective: Whether men have had CAI with male partners of unknown or discordant HIV status and the number of male partners with whom participants have had CAI in the previous three months will be assessed as part of the online, contact information update questionnaire at 9 months and as part of the computer-based questionnaire at the Off-Study visit.

STI screening will be conducted at the Off-Study visit as follows. Syphilis will be detected using rapid plasma reagin (RPR) and confirmed using the *Treponema pallidum* particle agglutination (TPPA) assay. Rectal, urethral, and pharyngeal gonorrhea and chlamydial infection will be detected using the Aptima Combo 2 (Gen-Probe Inc., San Diego, CA).

3.6 Participant timeline

Table 1 describes the schedule of evaluations for participants.

Table 1. Schedule of evaluations

	Screening	On-Study[1]	Quarterly	Off-Study[2]
Clinic Visit	X	X		X
Study Consent		X		
OraQuick training[3]		X		
Computer-based questionnaire		X		X
HIV EIA/NAAT[4]	X[5]	X		X
STI screening		X		X
HIV testing			X	
Online Questionnaire			X	
Blood volume (mL)	7	14		14
Visit length (min)	30	90		60

[1]The On-Study visit must occur within 30 days of the last negative HIV test.
[2]The Off-Study visit will be scheduled after 15 months of follow-up or at the time of the first confirmed HIV-positive test.
[3]For subjects randomized to Self-testing.
[4]EIA enzyme immunoassay; NAAT nucleic acid amplification test
[5]For subjects without recent HIV antibody testing only.

3.7 Sample size

This study is powered to detect a difference in the number of HIV tests reported by subjects in the two arms in the 15-month interval between the On- and Off-Study visits. To calculate the sample size, a control group equivalent to high-risk MSM attending the STD Clinic December 2002 until December 2006 was simulated. Excluding tests beyond the fourth, the mean testing frequency in this control group would be 1.25 tests per year. If, in the self-testing arm, 68% of participants have one additional test per year, the mean testing frequency will increase 0.58 tests per year. With 123 participants per arm, the study has 84% power to detect this difference of 0.58 tests even if we assume that 20% of participants will be either lost to follow-up or test HIV-positive during the study (an effective sample size of 197 participants). Table 4 uses these

assumptions to determine our power to detect differences using the t-test across a range of estimates of the effectiveness of self-testing at increasing testing in this population.

Table 2. Power to detect differences in the mean number of tests between the two arms at varying estimates of the effectiveness of self-testing with 123 subjects per arm and 20% loss to follow-up

Effect of home self-testing on number of tests during follow-up	Mean no. of tests		Increase in mean no. of tests (I-C)	Power
	Standard testing (C)	Home self-testing (I)		
68% test 1 additional time	1.25	1.83	0.58	0.84
50% test 1 additional time	1.25	1.68	0.43	0.58
34% test 1 additional time	1.25	1.54	0.29	0.3
68% test 2 additional times	1.25	2.38	1.13	<0.99
50% test 2 additional times	1.25	2.08	0.83	0.98
34% test 1 additional time + 34% test 2 additional times	1.25	2.11	0.86	0.99

3.8 Recruitment

Participants will be recruited from the PHSKC STD Clinic, Gay City Health Project Wellness Center, and other Seattle sites serving MSM through advertisements, clinician referral, and (STD Clinic only) waiting room recruitment as well as through advertisements on Facebook, Google Ads, and local websites targeting MSM and notices on listservs of local LGBTQ community organizations.

3.9 Intervention allocation

Participants will be randomly assigned to either the experimental or control group with a 1:1 allocation based on a computer-generated random number and using blocks of random size. The block sizes will not be disclosed to study staff involved in recruitment, enrollment, group assignment, or other participant interaction to ensure concealment. The randomization schedule will be performed by the study statistician, and group assignment will be enclosed in sequentially numbered, sealed envelopes by university staff not involved in the study. Participants will be asked to open the next envelope in sequence and read the group assignment to study staff.

3.10 Blinding

This is an open label study. Neither participants nor study staff will be blinded to the study group assignment of participants because it is impracticable to blind persons to an intervention involving access to HIV self-testing.

3.11 Data collection

Participants will complete self-administered computer-based questionnaires at the On-Study and Off-Study visits and after HIV testing during follow-up. These questionnaires address sociodemographic characteristics, HIV testing, sexual behaviors, substance use, and intentions to use self-tests. Two sexual behavior questions will be included in the online survey to obtain up-to-date contact information at 9 months of follow-up. These questionnaires are programmed in the University of Washington Catalyst web tool WebQ, which stores survey results securely online and accessible only to study staff. Data regarding study procedures, participant tracking,

and laboratory test results will be entered into study-specific databases accessible only to study staff.

Primary objective: The number of HIV tests received by participants during follow-up will be assessed by asking participants how many times they were tested for HIV while enrolled in the study as part of the self-administered computer-based questionnaire at the Off-Study visit. Participants will complete an event history calendar prior to the questionnaire in order to assist with recall[1].

Secondary objective: Whether men have had CAI with male partners of unknown or discordant HIV status and the number of male partners with whom participants have had CAI in the previous three months will be assessed as part of the online, contact information update questionnaire at 9 months and as part of the computer-based questionnaire at the Off-Study visit. These questions are based on survey questions from previous UW studies among MSM[2-4].

STI screening will be conducted at the Off-Study visit as follows. Syphilis will be detected using rapid plasma reagin (RPR) and confirmed using the *Treponema pallidum* particle agglutination (TPPA) assay. Rectal, urethral, and pharyngeal gonorrhea and chlamydial infection will be detected using the Aptima Combo 2 (Gen-Probe Inc., San Diego, CA). Laboratory results are sent by secure mail to study staff and then entered into a study database.

3.12 Participant retention

Once a participant is enrolled and randomized, study staff will make every reasonable effort to follow the participant for the entire study period. At the On-Study visit, all participants will be asked to provide extensive contact information, for themselves i.e. all possible addresses, phone numbers, and email addresses as well as social media screennames, and for at least one friend or family member for tracking purposes during follow-up. To minimize overall loss to follow-up and limit differential loss to follow-up between study arms during the study period, all participants will complete quarterly online surveys to maintain intermittent contact with the study coordinator and receive monetary compensation for their time. Participants will be asked only to provide updated contact information to minimize the potential impact on testing frequency. In order to obtain primary and secondary outcome data from participants who move out of the study area during follow-up and do not complete an Off-Study visit before relocating, these participants will be offered the opportunity to complete the Off-Study visit remotely. Participants completing remote visits will be asked to complete the computer-based questionnaire and event history calendar and to seek HIV/STI testing and either provide documentation of these results or sign a release of information so that study staff can request these results from the testing site.

3.13 Data management

Each study participant will be assigned a unique study identification number. Study visit records, laboratory requisitions, laboratory test results, and records of interim communications will be maintained in a file labeled only with the study ID and no other identifiable information. Contact information, printouts of contact update surveys, a participant-built 11-digit alphanumeric ID based on five questions, and any other identifiable information will be kept in a separate file labeled with the study ID. Information regarding screening, enrollment, participant preferences

regarding dried blood spots and test reminders, participant tracking, laboratory test results, event history calendar data, test results from releases of information from external healthcare providers, OraQuick test use, dried blood spot tracking and results, and other information from study visits entered by study staff into spreadsheets with study ID and no other identifiers; these spreadsheets will be accessible only to study staff. Self-administered computer-based surveys and online surveys completed at study visits and follow-up are programmed in the University of Washington Catalyst web tool WebQ, which stores survey results securely online and accessible only to study staff. These surveys will be linked to participants by beginning each survey with five questions to build the participant-built 11-digit alphanumeric ID. Surveys also include automatically generated submission IDs. Study staff will be responsible for maintaining a password-protected file matching study IDs with the participant-built ID and submission ID. WebQ produces downloadable Excel spreadsheets with survey data. These spreadsheets will be linked with other study data in SAS using the study ID. Survey data and laboratory data will serve as our outcome data. Study spreadsheets will be reviewed every 3-12 months (depending on the outcome of interest) by study staff for quality assurance purposes. Source documents, files, and records will be retained until the completion of data entry and cleaning, at which point personally identifying information collected by the study team will be destroyed, anonymizing the data. The anonymized data will be retained indefinitely.

3.14 Statistical methods

The iTest Study is designed as a randomized, controlled, open label single-center superiority trial with two parallel groups and a primary endpoint of number of HIV tests during 15 months of follow-up. The secondary objective is to determine whether HIV self-testing is non-inferior to standard HIV testing with respect to three markers for risk of HIV acquisition at 9 and 15 months of follow-up. A single interim analysis will be conducted by a data and safety monitoring board (DSMB) in March 2013 that will include a comparison of the primary endpoint using the O'Brien-Fleming stopping rule. The final analysis will be conducted when all participants have completed follow-up.

Primary objective: The number of HIV tests reported by participants in each arm at the Off-Study visit will be compared using the t-test. Using the O'Brien-Fleming stopping rule, the level of significance for the interim analysis will be 0.0046, while the significance level for the final analysis will be set at 0.048. Secondary analyses comparing (1) the proportion of participants who comply with PHSKC recommendations (i.e. test at least 4 times) during the study period and (2) the proportion of participants who report at least one test between the two arms will be conducted using Pearson's chi-square test or Fisher's exact test, as appropriate. If any baseline sociodemographic, behavioral, or clinical characteristics are imbalanced between the two groups, linear regression (for the number of HIV tests) and logistic regression (for proportions) will be used to adjust for confounding in secondary analyses. To address concerns about FDA approval of the OraQuick In-Home HIV Test contaminating the intervention, a stratified analysis comparing the number of HIV tests reported by participants between the two arms in the period prior to versus after commercial availability of this self-test in October 2012.

Secondary objective: In order to address concerns that the absence of risk reduction counseling in HIV self-testing will result in an increase in the risk of HIV acquisition, this objective is designed to determine whether men randomized to self-testing will demonstrate equivalent or

less risk of HIV acquisition when compared with men randomized to standard clinic-based testing, i.e. whether self-testing is non-inferior to standard testing with respect to risk. HIV self-testing will be considered non-inferior to standard testing with respect to the proportion of men reporting CAI with male partners of unknown or discordant status if the 95% confidence interval (CI) of the odds ratio comparing the odds of reporting non-concordant CAI among self-testers over the odds of reporting non-concordant CAI among standard testers is less than 2. We will calculate the 95% CI for this odds ratio using generalized estimating equations (GEE) logistic regression with exchangeable working correlation and robust standard errors to adjust for repeated measures. Self-testing will be considered non-inferior with respect to the number of reported male CAI partners if the 95% CI for the fold-difference in the number of partners between the two arms (self-testing - standard testing) is less than 2. GEE Poisson regression with robust variance will be used to calculate the 95% CI for this difference, adjusting for repeated measures. Self-testing will be considered non-inferior to standard testing with respect to STI prevalence if the 95% CI for the difference between the two arms (self-testing - standard) falls below 10%.

3.15 Data and Safety Monitoring

Annual summaries that detail study enrollment, withdrawals, reasons for withdrawal, adverse events, complaints and how they were handled, calls to the 24-hour contact number, and the performance of the HIV self-test as operated by study subjects at home will be compiled. These reports will be reviewed by the Protocol Chair and Co-Chair to determine if modifications to the research plan are necessary. Adverse events and other unanticipated problems will be reported to the IRB in real time to determine if modifications are necessary.

All subjects will be informed promptly of new information that might affect the risks of study participation and will be asked to sign the revised IRB-approved consent form or addendum consent form. If subjects do not have upcoming visits scheduled in the near future, they will be called to inform them about potentially serious information. Otherwise, they receive the information at their next visit.

Interim Analysis

A single interim analysis will be performed by the UW Center for AIDS Research (CFAR) Biometrics Core and forwarded to the data and safety monitoring board (DSMB) that has been constituted to oversee the conduct of the trial. Given the minimal risk nature of this trial, there will be one formal assessment by the DSMB in March 2013. The DSMB will review and evaluate the accumulated study data for participant safety, study conduct and progress, and efficacy. The interim analyses will include summaries of the baseline characteristics of the study participants, drop-out rates, and adverse events, in addition to the comparison of the effects of access to HIV self-testing at no cost on HIV testing frequency. Using the O'Brien-Fleming stopping rule, the two-sided level of significance for the interim analysis will be 0.0046, while the significance level for the final analyses will be set at 0.048. Based on these data, the DSMB will make recommendations to the study investigators concerning the continuation, modification, or termination of the trial.

Efficacy Review: The interim analyses evaluated by the DSMB will essentially constitute an efficacy review (defined as an increase in the number of HIV tests reported during follow-up).

Analyses of the association between the intervention and markers of the risk of HIV acquisition (Secondary Objective) will be conducted only at the completion of the trial, and will not be part of the interim analyses performed by the UW CFAR Biometrics Core.

Safety Review: Given the minimal risk nature of this trial, we have planned for one formal safety review by the DSMB, which will occur at the same time as the interim statistical analyses.

4. ETHICS AND DISSEMINATION

4.1 Human Subjects Considerations

Ethical Review: Ethical approval for the study will be obtained from the University of Washington Human Subjects Division (HSD). Study staff will make safety and progress reports to the HSD at least annually. Amendments to study procedures or materials will be submitted for HSD approval prior to implementation. Significant amendments to the protocol will be entered in the trial registry semiannually.

Informed Consent: Written informed consent will be obtained by study staff prior to enrollment in the study. The consent process will be conducted in a private room in the PHSKC STD Clinic. During the consent process, subjects will be presented information verbally as well as in writing. The information provided verbally will be similar to that contained in the consent form. The consent form will describe the study in detail, including the purpose of the study, the study procedures, duration and frequency of visits, types of information and specimens to be collected, the potential risks and benefits of study participation, and alternatives to study participation. No relevant information will be withheld. Subjects will be encouraged to ask questions and to discuss their participation with their personal physician, family, or friends and will be provided with a copy of the informed consent document prior to the enrollment visit to provide additional time for review. The signing of the consent form will be witnessed and dated. Each subject will be given a copy of the informed consent document if they are willing to receive it. The consent forms will be updated as necessary to reflect protocol revisions or new information.

Potential Risks: The major risks of participation include those related to study evaluations and self-testing. Home use of the OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test is not FDA-approved, and we have obtained an investigational device exemption from the FDA. Subjects randomized to HIV self-testing may experience stress regarding self-testing and may receive inaccurate results with self-testing. It is also possible that subjects will test individuals other than themselves. If subjects choose to collect a dried blood spot for back-up laboratory testing as part of self-testing, they may experience slight pain or discomfort from the fingerstick and anxiety associated with sending samples of their blood through the mail.

Subjects may experience increased stress as a result of having discussions about HIV infection, risk factors for acquisition of HIV infection, and past medical and sexual history. Subjects may learn that they are HIV-infected, which can cause psychological stress for the subject and his partner(s). Subjects with acute HIV infection will have physical stress in addition to the psychological stress because they may be symptomatic with HIV seroconversion. Physical examinations and screening for STIs may be uncomfortable. These activities may involve an

invasion of privacy. Blood draws can be uncomfortable and cause bruising, bleeding, fainting, or infection.

Subjects may perceive a loss of confidentiality by having records accessible to the study staff; study monitors, UW regulatory or fiscal oversight staff. In addition, subjects may be concerned about the loss of confidentiality if a diagnosis is made (e.g. syphilis or other bacterial STI) that is reportable by state regulations to the health department. Subjects diagnosed with HIV infection will not be directly reported to PHSKC but will be referred to the PHSKC One on One Program, where subjects will be reported if they register confidentially.

Protections against Risks: In order to minimize the risks of stress and receiving inaccurate results as a result of self-testing at home, subjects will be trained in detail regarding the performance of HIV testing, provided written instructions, and have access to study staff at any time through a 24-hour contact number. Subjects in the self-testing arm will also be offered the opportunity to send us a dried blood spot for back-up HIV testing. We will also inform subjects of the sensitivity of the test, the 'window periods' for both the OraQuick and RNA tests, symptoms of acute HIV infection, and problems with HIV detection during acute infection in order to minimize the risk that the accuracy of OraQuick in the first weeks after infection will be misunderstood by subjects in the home testing arm. Subjects who experience seroconversion symptoms will be encouraged to seek HIV testing at a site where RNA testing is available to reduce the likelihood that subjects receive only antibody testing at a time when the difference in accuracy between the two tests is greatest. Subjects who test positive using the home self-testing kit will call the 24-hour contact for counseling, help scheduling confirmatory testing, and any necessary referrals.

In order to minimize the likelihood that subjects will use the self-test on individuals other than themselves, we will inform subjects during the informed consent process, during the training for self-testing, and as part of the test kit instructions that we will be required to terminate their involvement in the study if we learn that they have shared a test kit. In addition, we will only provide one test kit per month unless the subject reports an invalid, misplaced, or damaged test. If a subject does test someone other than themselves, we will collect information regarding the experience if it occurs and terminate their involvement in the study.

To protect confidentiality, subjects will be given unique identification code numbers that will be used for all specimens and research records and will link questionnaires and HIV testing results. All interviews will be held in a private room in the PHSKC STD Clinic. All questionnaires will be completed using WebQ, a web-based survey tool developed at the University of Washington and approved as a research tool by the UW Human Subjects Division, and will only be identifiable by a study code. Baseline and end-of-study questionnaires will be self-administered by subjects, also in a private room at the PHSKC STD Clinic. The questionnaires for updating contact information and reporting HIV testing during follow-up will be self-administered online; subjects will be informed to use a computer where they feel comfortable answering sensitive questions and keep their responses private. Specimens sent to the laboratory for this study will be identified only by study code numbers, and the records linking the code to subject identifiers will be stored separately in a locked file cabinet and will be destroyed after study completion. We

will obtain a Federal Certificate of Confidentiality in order to further protect subjects' confidentiality.

Stress, anxiety, and depression (for subjects diagnosed with HIV infection) as a result of study participation will be minimized by periodic reassurance, careful explanation of study procedures and results, maintenance of an open, supporting attitude by all project personnel, and referral back to the subjects' primary care providers for further evaluation and care as needed. Routine clinical tests will be performed in CAP-certified laboratories (Washington State is CLIA-exempt) to ensure accuracy of the results. Immediate care for any medical complications due to the study procedures will be provided by the investigators within their areas of competence. Subjects will be responsible for costs of care if other medical services or hospitalization should be required. If subjects are diagnosed with HIV infection as part of the study, subjects will be referred for primary care. These studies will not provide HIV care or HIV treatment. Subjects who are diagnosed with treatable STIs as part of study procedures will receive care for these STIs, as appropriate. In the event that study procedures lead to another clinically significant diagnosis requiring intervention, the subject will be referred back to his or her primary care provider, or the investigators will assist the subject in identifying a source of medical care if they have not been in care.

Risks to HIV-seronegative personnel of acquisition of HIV-1 through accidental exposure will be minimized by rigorous adherence to the institution's infection control procedures including mandatory training in blood-borne pathogens. Laboratory staff members receive additional training in appropriate personal protective equipment, and infectious specimens are processed in a BSL-2+ room within a biosafety cabinet.

If a subject suffers harm as a direct result of this study, study staff will either treat the subject on an emergency basis at no cost to the subject or refer the subject to appropriate care, in which case payment will be made within the limits of the University of Washington compensation plan.

Potential Benefits: Subjects will receive extensive education about HIV infection and HIV prevention. The subjects will have laboratory and clinical assessments that may detect HIV at an earlier, more treatable stage. Procedures will be cost-free. Societal benefits will accrue from the knowledge gained from this research. Potential benefits include increased understanding of HIV infection and HIV testing strategies. This knowledge may help improve the health status of persons with HIV and prevent other individuals from acquiring HIV infection.

4.2 Declaration of Interests

JDS: Alere provided Determine HIV-1/2 Ag/Ab Combo tests and controls for a study comparing the performance of different HIV tests during early HIV infection.

4.3 Access to Data

The Protocol Chair and Co-Chair will manage access to study data. All study investigators will have access to cleaned datasets upon request. Project data sets will be housed on a secure UW server. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

4.4 Dissemination Policy

The study investigators retain the sole right to present publicly and publish the data from all portions of the study. A letter summarizing study results will be distributed to study participants and local stakeholders following HSD approval.

5. REFERENCES

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Supplemental Digital Content 2. Effects of access to HIV self-testing on HIV testing frequency during follow-up, stratified by time of study participation relative to when the OraQuick In-Home HIV Test was introduced to the U.S. market

Time of study participation[1]	Self-testing arm		Control arm		Mean difference in no. of HIV tests[2,3] (95%CI) [Self-testing *v* Control]	p-value
	N	Mean no. of HIV tests[2]	N	Mean no. of HIV tests[2]		
Pre-approval	39	4.9	38	3.6	1.3 (0.004-2.6)	0.049
Pre- and post-approval	31	5.8	27	3.4	2.4 (0.8-4.1)	0.005
Post-approval	28	5.4	34	3.8	1.6 (0.4-2.7)	0.007

CI = Confidence interval. [1]Participants were classified based on when their participation occurred relative to October 1, 2012, when the OraQuick In-Home HIV Test became available for purchase in the U.S. Participants whose entire participation occurred prior to this date were classified as "pre-approval", those who enrolled prior to and completed the study after this date as "pre- and post-approval", and those who enrolled after this date as "post-approval". [2]Self-reported number of HIV tests during follow-up, as measured at the end-of-study visit. [3]We found no evidence that the effect of access to HIV self-testing on HIV testing frequency differed across the three time periods (linear regression test for interaction, p=0.50) or between pre-approval vs. post-approval alone (p=0.29).

Supplementary Digital Content 3. Effects of access to HIV self-testing on HIV/STI testing frequency, unadjusted vs. adjusted estimates

	Mean no. of tests during follow-up		Difference in mean no. of tests (95% CI)[1] [Self-testing – Control]			
Outcome	**Self-testing**	**Control**	**Unadjusted**	**p-value**	**Adjusted[2]**	**p-value**
Total HIV tests	5.3	3.6	1.7 (0.9 to 2.5)	<0.001	1.8 (1.0-2.6)	<0.001
Clinic-based HIV tests	1.4	3.6	-2.2 (-2.7 to -1.7)	<0.001	-2.0 (-2.6 to -1.5)	<0.001
STI tests	2.3	3.2	-0.9 (-1.5 to -0.3)	0.004	-0.8 (-1.4 to -0.2)	0.01

STI = sexually transmitted infection. [1]Calculated using linear regression. [2]Adjusted for characteristics that were not balanced at baseline between men in the two study arms, including: STI diagnosis at enrollment visit, education, number of HIV tests in the last year, and Hispanic/Latino ethnicity.

Supplemental Digital Content 4. Effects of access to HIV self-testing on HIV risk during follow-up, unadjusted vs. adjusted estimates

Marker for risk of HIV acquisition	Measure	Point estimate of difference (95% CI) [self-testing vs. control]		Non-inferiority bound
		Unadjusted	Adjusted[1]	
Non-concordant CAI, last 3 months (%)	Odds ratio	1.07 (0.61 to 1.90)	1.06 (0.59 to 1.91)	2.00
No. male CAI partners, last 3 months (mean)	Incidence rate ratio	0.92 (0.64 to 1.33)	1.02 (0.69 to 1.49)	2.00
Bacterial STI diagnosis at end of study (%)	Risk difference	-6.8% (-16% to 1.6%)	-5.4% (-13% to 2.7%)	+10%

STI = sexually transmitted infection (early syphilis, gonorrhea, or chlamydial infection). CAI = condomless anal intercourse. CI = confidence interval. [1]Adjusted for characteristics that were not balanced at baseline between men in the two study arms, including: STI diagnosis at enrollment visit, education, number of HIV tests in the last year, and Hispanic/Latino ethnicity.