Official Title: eTest: Real-time, Remote Monitoring System for Home-based HIV Testing Among High-risk Men Who Have Sex With Men

NCT Number: NCT03654690

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BROWN UNIVERSITY
INSTITUTIONAL REVIEW BOARD
HUMAN RESEARCH PROTOCOL

Protocol Title: eTest: Real-time, remote monitoring system for home-based HIV testing among high-risk men who have sex with men
Principal Investigator: Tyler B. Wray, Ph.D.
Department: Center for Alcohol and Addiction Studies
Funding Source (if no external funding for the project, enter "University")**:** University
If externally funded, Coeus Institute Proposal # for the project:

(1) Attach to this form the information required for a complete protocol, as outlined on the IRB Form #1 Instructions & Information pages. In addition, please review the document "What Makes a Complete Protocol."

(2) Select the appropriate type and category number of review. See descriptions of expedited categories. If no expedited categories completely describe the proposed research, select "Full Board.")

☒ **Expedited #** ☐ **Full Board**

(3) **Investigator Conflict of Interest Statement:**
The *Brown University Conflict of Interest Policy for Officers of Instruction and Research* *("COI Policy")* defines the term "Investigator" as "the project director or principal investigator and any other person, regardless of title or position (e.g., full or part-time faculty member, staff member, student, trainee, collaborator, or consultant), who is **responsible** for the **design, conduct, or reporting** of sponsored research." Using this definition of "Investigator," please ensure that all Investigators on this protocol answer questions 3(a) and 3(b) below [attach additional sheets for any Investigators who are not the PI; they only need to answer 3(a) and 3(b)]:

(a) Is your annual Assurance of Compliance form (and, if necessary, reporting form) accurate and up-to-date as of the time of this submission, as required by the COI Policy? (You may access the system here to confirm.) ☒**YES** ☐**NO**
(b) Do you have a significant financial interest (SFI) that is related to this research protocol? "Related" could mean the research involves products, technology, intellectual property, or services made, owned, or provided by the entity/ies in which you have an SFI and/or that the SFI could be affected by the proposed research or its results. ☐**YES** ☒**NO**

Principal Investigator certifies to the following: ***(1)*** The rights and welfare of the participants are adequately protected. ***(2)*** The risks to an individual are outweighed by the potential benefits to him/her or by the importance of the knowledge to be gained. ***(3)*** This protocol is accurate and complete; if the project scope or design is later changed, the PI will resubmit for review. ***(4)*** All research personnel, including the PI, has been, or will be, adequately educated in human research protections prior to beginning work on the project.

Principal Investigator signature: _____ **Date:** 04/03/18

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(Advisor's signature is required for all graduate/medical student projects.)
Advisor certifies to the following: Advisor has read the protocol and approves of the project.
Advisor's signature: _____ **Date:** _____
Print name:

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Undergraduate student investigator signature: _____ **Date:** _____
Print name: (optional signature)

For IRB Use Only
FULL BOARD PROTOCOLS **-** Institutional Review Board Members: If approving the proposed project, please certify to the best of your knowledge to the following: ***(1)*** IRB Member is familiar with the above described proposed research. ***(2)*** The rights and welfare of the research participants will be adequately safeguarded by the procedures described. ***(3)*** The potential benefits justify the risks involved. ***(4)*** IRB Member has no vested interest in the project.
IRB Member Signature: _____ Date: _____

Signature of the Authorized Official of the IRB: _____ **Date:** _____

Protocol Checklist and Submission Procedures

This page must be COMPLETED and INCLUDED as page #2 of your submission

To ensure the quickest turnaround time possible, please prepare your protocol for IRB review (full board or expedited) with all the following information that is applicable to your project, number the pages and note the page numbers of each item on the checklist. Refer to the following instructional pages for more information about the required elements of an IRB protocol.

Protocol component	Included?	Page number(s):
1. IRB Form #1	☒Yes	
2. Lay Summary	☒Yes	
3. Protocol Narrative:		
Aims & Methodology	☒Yes	
Informed consent procedure	☒Yes	
Consent/Assent documents/scripts	☒Yes ❑ N/A	
Risks and Benefits	☒Yes	
4. Attachments (if applicable):		
a) Interview/survey/focus grp instruments	☒Yes ❑ N/A	
b) Letters/e-mails to participants	☒Yes ❑ N/A	
c) Recruitment materials	☒Yes ❑ N/A	
d) Letters of support/permission	☒Yes ❑ N/A	
e) Other IRB approvals	❑Yes ☒ N/A	
f) Data Use Agreements	☒Yes ❑ N/A	
g) Protocol addenda/appendices, as needed	❑Yes ☒N/A	
h) Funding application	☒Yes ❑ N/A	

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Protocol Submission Procedures

Full Board Protocols: Submit the complete (as identified above) protocol to the Human Research Protection Program (HRPP) by e-mail in ONE PDF file to IRB@brown.edu, in sufficient time to meet the agenda deadline (see the HRPP meeting deadline page for upcoming IRB meeting dates and submission deadlines).

Expedited Protocols: There is no specified deadline for submission of Expedited Protocols. Review time varies depending upon the project. The average review time is approximately 4 weeks. Please submit the complete (as identified above) protocol to the HRPP by e-mail in ONE PDF file to IRB@brown.edu, with sufficient time to allow for review and revisions, if necessary.

{Note that the IRB (not the investigator) makes the final determination of whether a protocol is full board or expedited. Thus, full board review may be necessary even if you suggest expedited review in your protocol.}
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Project Title: **Real-time, remote monitoring system for home-based HIV testing among high-risk men who have sex with men**

Principal Investigator: **Tyler B. Wray, Ph.D.**

Co-Investigators: **Philip Chan, MD; Lenadro Mena, MD, James Brock, MD; Jeffrey Klausner, MD; Jack Needleman, Ph.D.**

A. Lay Person Summary

HIV disproportionately affects men who have sex with men (MSM) in the United States, and new infections continue to increase particularly among African American (AA) and Hispanic/Latino (H/L) MSM. Past studies estimate that up to 50% of these new infections originate from the approximately 20% of MSM who are unaware of their status. Expanded HIV testing can produce reductions in incidence when implemented on a broad scale by facilitating earlier diagnosis and treatment. Rates of HIV testing are particularly low among AA and H/L MSM, and innovative approaches to encourage testing may help address high incidence in these men. Home-based, self-testing (HBST) for HIV offers considerable promise for increasing the number of MSM who are aware of their status by overcoming key barriers to clinic-based testing, such as inconvenience and confidentiality concerns. HBST may also be particularly well-suited for AA and H/L MSM, given that stigma and mistrust of medical care contribute to low testing rates. Despite its promise, however, many are concerned that HBST does not sufficiently connect users with critical post-testing resources, such as confirmatory testing and care among those who test positive, and that these limitations may result in delayed linkage to care. Existing, FDA-approved HBST kits provide a free, 24-hour helpline that offers these services to those who seek it, but few users do, and this "passive" approach may miss critical opportunities to engage with MSM for further prevention services.

To address these challenges, we developed a mobile health platform ("eTEST") that uses internet-of-things (IoT) technologies to monitor when HBST users open their tests in real time, allowing us to provide timely, "active" follow-up counseling and referral over the phone after they do so. In a pilot study, we show that providing HBST by mail at regular intervals boosted rates of any/repeat HIV testing among high-risk MSM compared with clinic-based testing reminders. Moreover, those who received follow-up phone counseling after HBST were more likely to receive risk reduction counseling, to consult with a medical provider about PrEP, and to initiate PrEP. Given these promising results, the proposed research will conduct a fully-powered efficacy trial of this approach in areas with large populations of AA and H/L MSM and high HIV incidence: Jackson, MS, Los Angeles, CA, and Boston, MA. High-risk MSM who have not tested for HIV in the last year will be recruited from MSM-oriented "hook-up" mobile apps, and assigned to receive either (1) HBST with post-test phone counseling/referral ("eTEST" condition), (2) "standard" HBST without active follow-up, or (3) reminders to get tested for HIV at a local clinic ("control" condition) at three month intervals over the course of 12 months. We will explore the impact of the eTEST system on key outcomes, including rates of HIV testing, receipt of additional HIV prevention services, and PrEP initiation, compared with standard HBST or clinic-based testing reminders alone. We will also explore the cost effectiveness of the

eTEST system under various scenarios compared with relying on traditional, clinic-based testing alone.

B. Protocol Narrative

B.1 Significance and Specific Aims of Project

Significance. Although overall HIV incidence in the US has remained stable in recent years, new infections continue to increase in certain groups of men who have sex with men (MSM)1. In 2014, MSM accounted for 67% of all new HIV infections2, a rate that has steadily risen in recent years30. New infections are especially high among African American (AA) and Hispanic/Latino (H/L) MSM. Recent surveillance data suggests that, if current incidence trends continue, 1 in 2 AA MSM, and 1 in 4 H/L MSM will be diagnosed with HIV in their lifetimes31.

One source of new HIV infections stems from those who are aware they have HIV but who are not virally suppressed. However, another major source is the estimated 20% of MSM who are infected but unaware of their status32. Past studies suggest that this scenario accounts for up to 50% of new infections5; 6, prompting calls to increase the access and availability of HIV testing33. Despite their elevated risk, less than 60% of MSM report having been tested in the last 12 months, and only 20% have been tested more than once in the past year34; 35. AA and H/L MSM are also twice as likely as White MSM to have never tested in their lifetime34.

Testing is a cornerstone of HIV prevention efforts, since it can facilitate early diagnosis and treatment (i.e. "test and treat")36. Studies show that this approach can reduce HIV incidence when implemented broadly37-39, in part by reducing the time between infection and diagnosis, which averages 2.6 years in some areas40. Expanding testing is a particularly important step in reducing new infections among AA and H/L MSM, since those who are unaware of their infection are key drivers of incidence in these groups3; 4. These findings suggest that innovative approaches to expanding testing are needed, particularly among AA and H/L MSM.

Use of gay-oriented "hookup" apps to meet sexual partners is nearly ubiquitous among single MSM, with >90% reporting sex with a partner met online in their lifetimes41, and 70-85% having met their most recent partner online41-44. Young MSM are a particularly high-risk group2, and may be more likely to meet partners this way45-48. Studies also suggest that online sexual partnerships are frequently sources of new HIV and STI infections49; 50. Our past work showed that 60% of MSM newly diagnosed with HIV met partners online in the past year49. The increasing number of MSM who meet partners online has raised concerns about the difficulties this may pose for engaging MSM through traditional prevention efforts (e.g., in-person outreach and clinic-based testing)43; 51; 52. At the same time, use of dating apps/websites by a vast majority of high-risk MSM suggests that prevention programs may be able to reach more of these men now than ever before through online outreach62; 63, including subgroups that often evade in-person outreach, like AA and H/L MSM and MSM that do not identify as gay. However, to capitalize on the opportunity, new strategies are needed to link these men with HIV testing and other prevention services that go beyond clinic-based testing.

In July 2012, the first rapid, home-based self-test for HIV (HBST) was approved by the FDA (OraSure® Technologies, Bethlehem, PA). This test uses oral fluid sampling, produces results in 20 minutes, and can be completed entirely by consumers. As a compliment to clinic-based testing, HBST has the potential to reach more high-risk MSM who test infrequently. Past studies show that the most prominent obstacles to clinic-based testing among MSM were concerns about confidentiality and inconvenience (e.g., travel, wait times)53; 54. Others show

that the vast majority of MSM, and especially young MSM and those who have never tested, would prefer HBST and feel they would test more often with HBST7-9; 53; 55-57. Further, HBST may be particularly well-suited to increase testing among AA and H/L MSM, given that stigma and distrust of traditional medical services are key obstacles to clinic-based testing for these men58-60. These findings underscore HBST's potential for overcoming barriers to testing and for encouraging those who test infrequently to do so more often. Using HBST to encourage more frequent, regular HIV testing could facilitate earlier diagnosis and linkage to care, thereby improving disease outcomes61 and reducing onward transmission62. For these reasons, the World Health Organization has recently recommended HBST for high-risk populations, and suggested that it may be key to reaching its target of diagnosing 90% of those who have HIV63. One strategy for increasing HIV testing among high-risk MSM involves providing free HBST through the apps/sites they already use. Our past studies15; 18; 64 show that using these apps to inform users about HBST, conduct a brief risk assessment, and send an HBST through the mail is acceptable and feasible. Moreover, Elliot et al.65 also demonstrated that sending HBST to app users successfully detected new HIV infections, with 77% of new diagnoses made at CD4 counts >350 cells/μL, suggesting that HBST might facilitate early diagnosis. Together, this work shows that providing high-risk MSM who use hookup apps with HBST could be an effective way to encourage them to test and may detect new infections earlier. However, these efforts have primarily been designed to encourage a single test. Mobile/web prevention tools could be an effective way to seamlessly connect with high-risk MSM via the hookup apps/sites they already use and to keep them engaged over time by encouraging them to test regularly and linking them with other prevention resources afterward.

In exploratory work supported by NIMH (R21MH109374), we used Internet-of-Things (IoT) and mobile technologies to develop a "smart" HBST kit that monitors when recipients open the kits, enabling an HIV test counselor to reach out to provide timely follow-up phone counseling/referral. The system (called "eTEST") uses a Bluetooth low energy beacon (Estimote LocationTM beacon) with an ambient light sensor that is placed inside each test kit's enclosure (see Figure 1). Smartphone applications (both iOS and Android) installed on recipients' phones then monitor the proximity of the beacon to the phone and the amount of light reaching it (>1 lux) to automatically determine whether the recipient has opened the test enclosure. When these conditions are met, the app then updates a Structured Query Language (SQL) database on a central server and sends push notifications to users reflecting that they should expect a call from a counselor. The SQL database also issues notifications to a team of paraprofessional HIV test counselors, who place follow-up phone calls to users to conduct post-test counseling and provide referrals to users for other services (e.g., STI testing, PrEP consultation). The system requires no intervention from users to work, and successfully detects kit opening events even when the app is in the background, has been "killed," or the user's device is in sleep mode. "Pings" to the central server from the eTEST app also allow the HIV test counselors to monitor whether specific users have the app on their devices. See Fig. 2 for eTEST system flow.

In our small pilot study, we enrolled 73 participants, 92% of which have been retained to date. Response rates to online surveys have been excellent, with an average monthly completion rate of 94% (*SD*=4.3, 86%- 100%). Of those in the eTEST group, 75% have kept the app downloaded on their phones over the average of 5 months they have been enrolled so far. All but two of these participants were contacted and successfully re-downloaded the app to continue the study. The eTEST system has successfully detected 91% of opening events among eTEST

participants so far. Follow-up counseling/referral phone calls were successfully placed for all detected openings and only four were not reached within 24 hours. All participants successfully reached for follow-up reported having taken the test **minutes** after opening it, suggesting that monitoring the kit's **opening** serves as a reasonable marker of when they **took** the test. Figure 3 shows study outcomes to date. These data show that 96% of those in the eTEST group have tested for HIV at some time during the study period, compared with 90% for standard HBST, and 62% for control. Among the 63% of participants who have completed Month 5 of the study, repeat testing rates (reporting testing during **both** of the first two 3-month periods) were 92% in eTEST, 54% in standard HBST, and 46% in control. Rates of testing for other STIs were modestly higher in the HBST conditions, but this difference is difficult to interpret due to the small sample size and may not be meaningful.

Over 72% of eTEST participants received risk reduction counseling during the study period (control=18%, standard HBST=15%). While PrEP was not an explicit focus of the follow-up phone calls, 25% of eTEST participants reported having consulted with a physician about PrEP and 10% reported having started PrEP as a result, compared with 4% who sought consultation and started PrEP in the control group. While AA and H/L participants comprised only 21% of this sample, over 75% of those assigned to HBST conditions tested for HIV at some point during the study period, compared with 43% in the control condition. Moreover, 67% reported testing during both the first two quarters of the study so far, compared with 33% in the control condition.

Together, these studies suggest that providing HBST at regular intervals could be a promising tool for increasing HIV testing rates and frequency, especially among particularly high-risk populations of MSM, such as those who meet partners online and those who test infrequently. Our preliminary data further suggests that offering more active, phone-based counseling and referral services alongside HBST could help encourage these men receive other key prevention services. However, no fully-powered studies have explicitly tested these hypotheses to date. While our pilot work on eTEST has begun to explore these issues, limitations in the size, scope, and location of this study precludes firm conclusions about the utility and impact of HBST and eTEST as a potential component of community testing initiatives. (1) The results above are from a pilot project in which it was only feasible to recruit a small, local sample with a shorter study period (7 months) than is likely realistic. As such, the next steps are to test this promising approach as part of a full efficacy trial that involves following a much larger sample over a more realistic timeframe. (2) Programs encouraging regular HIV testing may also have the most impact in regions/populations that are highly affected by HIV74, such as those with larger populations of AA and H/L MSM. Our pilot sample, recruited exclusively in Providence, consisted of only 21% AA and H/L MSM. As such, it is critical to extend this work to explore the effects of eTEST and HBST in areas/populations with high HIV incidence, such the Deep South and West Coast, where large populations of AA and H/L MSM reside74. (3) Finally, to provide the most realistic picture, it is also critical to examine eTEST's effects when it is deployed in a manner consistent with its goal: To provide users of online "hookup" apps a pathway for testing more regularly, by providing them the ability to test on their own, without in-person meetings. Thus, another important next step involves developing an architecture for linking users of online hookup sites/apps directly to the eTEST system (see Section 3C.2.).

Importantly, our pilot data also shows that connecting with high-risk MSM through eTEST may be a key opportunity to also link them with PrEP. Daily oral PrEP is now recommended for MSM who are at high risk for HIV acquisition75, given strong evidence of its efficacy for preventing infection76-78. Despite its promise as a prevention tool, uptake in the US has been slow79, likely due to barriers such as limitations in awareness, access, and trust80-83. Uptake of PrEP among AA and H/L MSM has been especially slow, with racial/ethnic disparities emerging across the PrEP care continuum83; 84. In our pilot, all participants met risk criteria for PrEP, since all reported CAI with a casual partner in the last six months75. While post-test follow-up calls did not include discussion of PrEP, many participants asked about it during these calls, and several later consulted with medical providers about starting PrEP. Given this, we believe that follow-up calls could facilitate ongoing discussions about PrEP with participants while on the eTEST program, and provide opportunities to ask questions, consider its benefits/risks, and connect users with PrEP providers. In another study we conducted, a substantial portion of MSM who were educated about PrEP were lost to follow-up before initiating it19. Increasing contact with MSM who are candidates for PrEP may improve their engagement with PrEP care. A more personal approach that involves establishing trust and encourages two-way communication may also be especially important for engaging AA and H/L MSM, since mistrust of medical care is a key barrier in these groups that likely contributes to existing racial and ethnic disparities in PrEP use85; 86. Past studies also showed that awareness and willingness to use PrEP is particularly low among AA MSM who test infrequently83, suggesting that offering PrEP counseling alongside HIV testing may reach a critical subgroup.

Specific Aim 1: To test whether the eTEST intervention results in higher rates of (a) initial and follow-up HIV testing, and (b) receipt of additional prevention services after testing (e.g., STI testing, risk reduction counseling, safer sex supplies) compared with standard HBST and reminders for clinic-based testing among MSM in three US regions with large AA and H/L MSM populations. As an exploratory aim, we will also examine whether receiving HBST helps detect more infections during the study period and reduces the time to diagnosis among those receiving reactive results, compared with clinic-based testing alone.

Specific Aim 2: To test whether providing focused information/counseling about PrEP during eTEST contacts results in more participants (a) consulting with medical providers about PrEP and (b) initiating PrEP. We will define a PrEP care continuum, including the number of MSM who meet clinical indications for PrEP, the number who are interested in and are linked to care, the number who are prescribed PrEP, and the number who initiate PrEP in each condition.

Specific Aim 3: To assess the cost-effectiveness of the eTEST system for improving rates of HIV testing compared with clinic-based testing alone. We will use mathematical models to estimate whether the eTEST system (and HBST) can be cost effective under various scenarios (e.g., testing intervals).

The proposed research will provide a robust test of the feasibility, efficacy, and value of home-based testing programs with post-test follow-up in communities with large populations of AA and H/L MSM that are highly affected by HIV. It is also among the first studies in the US to leverage HBST to engage difficult-to-reach populations in care. Results can also inform efforts to seek high-risk MSM and engage them in PrEP services.

Overview of Research. Given these issues, the proposed research involves conducting a fully-powered efficacy test of HBST and the eTEST system's effects on rates of any/repeat HIV testing, use of other prevention services (e.g., STI testing, HIV risk reduction counseling), and PrEP linkage/initiation, compared with "standard" HBST and reminders for clinic-based testing, among high-risk MSM in three regions in the US: The Deep South (Jackson, MS), West Coast (Los Angeles), and Northeast (Providence/Boston). High-risk MSM (*N*=2000, *N*=666 per metro) who have not tested in the last year will be recruited online using an interactive web application. Participants will be randomly assigned to one of three arms that involve receiving one of the following at baseline, 3, 6, and 9 months: (1) HBST with phone follow-up (eTEST condition), (2) standard HBST (no follow-up), or (3) reminders for clinic-based testing only (control). Only enhanced eTest participants will be provided with the eTEST app, which will monitor the status of HBST kits and facilitate phone follow-up. Control participants will receive text messages at quarterly intervals, reminding participants to get tested in a clinic. Participants in the standard HBST condition will receive their HBST in the mail when it is time for their quarterly tests. All study participants will have access to information that may be generally helpful (e.g., information about HIV, testing, and a testing clinic locator) and are already publicly available. Throughout the study, all participants will complete online questionnaires assessing key outcomes each quarter, which will be confirmed by reviewing clinical records in each local area when possible. Analyses will assess eTEST's efficacy within and across regions, as well as the cost-effectiveness of these strategies compared with relying on clinic-based testing alone.

B.2 Participant Population

Eligible participants will be (1) biological males, who (2) report any of the following in the past six months: anal sex without condoms outside of a monogamous partnership with a recently tested, HIV-negative male, having been diagnosed with an STI, or being in an ongoing sexual partnership with an HIV-positive male, and who (3) are not currently on PrEP. We chose to focus our study on male participants because epidemiological evidence suggests that MSM are disproportionately affected by HIV, and thus in need of tailored interventions for increasing HIV testing30; 102. These criteria are inclusive of transgender women, however. While we realize that there may be too few transgender participants to facilitate subgroup analyses, we elected to be inclusive because of the clear public health relevance of these individuals103. Risk criteria were chosen to align with DHHS's PrEP criteria104 to allow comparisons with other PrEP studies. Eligible participants will also (4) have not tested for HIV in the last 12 months, (5) have a stable residence in one of the site metros where they can securely receive packages, (6) use an iOS/Android smartphone with a data plan or home wifi, and (7) be fluent in either English or Spanish. We will strive to recruit AA and H/L MSM at rates similar to each site's general population, but will also implement procedures specifically to attract/retain AA and H/L MSM, including consulting with local ethnic/minority community advisors about recruitment, targeting apps catering to AA and H/L MSM (e.g., Jack'd), matching race/ethnicity in ad materials, emphasizing participants' rights and community benefits in informed consent, and recruiting AA and H/L staff/counselors105; 106.

B.3 Recruitment Procedures

Ads will be placed with several MSM-oriented "hookup" apps (e.g., Grindr, Scruff, Jack'd) to recruit participants into the study. Ads will display to users who login to the apps within 30 miles of each metro. Clicking on the ad will direct users to a landing page for the eTEST study, where users can learn about the study and its requirements. A brief questionnaire will assess eligibility criteria, and those eligible will then be directed to register for the study, which will involve providing informed consent, basic personal information, and baseline questionnaire data (see Human Subjects for more details about online informed consent). The web app will then randomize participants to one of the three arms. Finally, the web app will then walk participants through downloading the eTEST app from the Google Play or iTunes stores only if they were assigned to the enhanced eTest condition. Access to the eTEST app will be restricted to users registered in the eTEST web portal who are directed specifically from that site. Participants will also be encouraged to keep the app downloaded on their phone throughout the study period and will be encouraged to register any changes in their mailing address or smartphone information (number, phone OS) as soon as possible, either through the eTEST app, web portal, or by notifying study staff.

Once users have registered, staff will conduct a brief introductory call with all participants to ensure that their information is correct and that they understand the study's requirements. After successfully completing this call, study staff will mark these participants as 'fully enrolled,' activating them in the study database.

B.4 Design and Methods

In the study phase, 2000 high-risk MSM who have not tested in the last year will be recruited from three metro areas, Providence/Boston, Jackson, MS, and Los Angeles, CA, using ads on MSM-oriented, geolocation-based mobile "hookup" apps. They will be randomized to receive one of the following at three month intervals over the course of a year: (1) HBST with remote monitoring and post-test phone counseling/referral (eTEST condition), (2) standard HBST without active follow-up, or (3) reminders to get tested for HIV at a local clinic, delivered via text messages (control condition). We chose a three month retesting interval (HBST/reminder) to align with the CDCs most stringent recommendations for high-risk MSM98. During the study period, participants will complete quarterly surveys online. At 12 months, participants will be asked to present to a local clinic to provide a blood sample for HIV testing, to facilitate exploratory analyses comparing the number of infections successfully detected in each group and the "time to diagnosis" in each condition (see 3C.3.5.2 for more detail).

Experimental Conditions

Only enhanced eTest participants will download the eTEST app. For these participants in the eTEST group, four HBST kits will be fit with BLE sensors and sent to participants. Follow-up calls will be made to these participants within 24 hours of opening their test to provide post-test counseling, referral for services, and a focused discussion on PrEP. In the standard HBST condition, four standard HBST kits will be sent at the same intervals, but will not be monitored and no follow-up calls will be provided. Standard participants will have a list of local resources (in Boston/Providence, L.A., or Jackson) depending on where participants are located included in the box with their test kit. This list of resources includes HIV/STD testing clinics, alcohol/drug and mental health treatment referrals, and the number for the national suicide prevention hotline,

as well as study staff contact information. These kits also, include a 24 hour helpline that participants can call with any questions or needs. In the control condition, participants will be reminded to get tested at a local clinic via text messages. Texts will link to the list of local clinics near them that conduct HIV testing, as well as their contact information/hours.

Measures

After enrolling, participants will complete a baseline questionnaire assessing demographics, language barriers, immigration status, past HIV/STI testing history, recent use of other prevention/sexual health services, recent sexual behavior107-114, alcohol/drug use108; 115, and mental health116. These data will be useful for exploring barriers to testing, and changes in these variables over the study period.

Quarterly online questionnaires.

Participants will also complete online questionnaires each quarter during the 12-month study period, which will be staggered and assigned one month after each testing interval to minimize possible conditioning effects. These surveys will assess HIV testing since the last study assessment, including whether they tested, how/where they tested, what their results were, whether each test was associated with PrEP care, or reasons for not testing. This approach will allow us to track contamination across conditions, or the extent to which those assigned to the control condition used a HBST or those in HBST conditions tested at a clinic. Questionnaires will also assess whether participants were referred for additional prevention services (e.g., STI testing, HIV risk reduction counseling), and whether they received these services since the last survey. Items will also assess whether participants consulted with a medical provider about PrEP in the last month, and if so, their provider's information and whether they were prescribed PrEP. Finally, as a compliment to passive app data, questionnaires will also assess app usage.
These surveys will also assess constructs relevant to the behavioral, emotional, and social effects of HBST, including sexual risk behavior (online Timeline Follow Back106-114; 125), emotional health (PANAS-X116), health empowerment117; 118, and social support119. Finally, these surveys will also assess financial strain120, insurance121, housing instability122, stigma100; 101, and medical mistrust123, given evidence that these factors may be barriers to testing124-128.

Clinic-based HIV/STI testing.

At the end of the 12-month study period, all participants in all conditions will be asked to present to designated clinics for in-person HIV testing in exchange for a bonus payment ($50). Encouraging participants in this way can help ensure that we have at least one accurate HIV test result for each (since some may elect not to test at all during the study period, regardless of condition). Results will allow us to more confidently estimate the number of new infections that were successfully detected or missed with HBST versus clinic-based testing reminders. For those who test positive, basic data from the sample (e.g., viral load, CD4 count at the time of confirmatory testing) will be collected from the medical records of each participant, provided they have signed a release. These data will permit us to estimate the "time since infection" for each participant diagnosed with HIV129, allowing us to address our exploratory hypothesis that HBST could facilitate earlier diagnosis compared with encouraging clinic-based testing alone.

Clinic records.

We will also review clinical data for each participant to compare with self-report data on HIV testing, STI testing, and PrEP uptake. We will obtain a signed HIPAA release to review the records of area clinics where participants reported receiving these services. Data on verified service use will be compared across conditions to explore potential differences. While we realize that this data may be incomplete (especially given that some may elect to test at certain sites anonymously), we believe that collecting as much corroborating data as possible will serve as an important compliment to self-report data. Data collected is limited to:

- Date of HIV test
- Viral load
- CD4 cell count
- Type of HIV test (blood vs. antibody)
- HIV status
- Whether the patient received counseling to reduce their risk for HIV
- Date of each STD test
- STD tested
- Test results
- Whether the patient spoke to a provider about PrEP
- Whether the patient was prescribed PrEP

*Data Use Agreements will be put in place to allow staff at each study site access to the study database (saved on Brown's servers) in order to verify service use and enter data collected.

Individual interviews.

RAs at each site will contact participants via phone at the end of the study to conduct a 30-minute individual interview about their experience using the eTEST app and HBSTs (if applicable). Interviews will inquire about the strengths/drawbacks of HBST versus clinic-based testing, their perceptions of the app and its features, and their preferences for follow-up/referral.

Procedure

Ads will be placed with several MSM-oriented "hookup" apps (e.g., Grindr, Scruff, Jack'd) to recruit participants into the study. Ads will display to users who login to the apps within 30 miles of each metro. Clicking on the ad will direct users to a landing page for the eTEST study, where users can learn about the study and its requirements. A brief questionnaire will assess eligibility criteria, and those eligible will then be directed to register for the study, which will involve providing informed consent, basic personal information, and baseline questionnaire data (see Human Subjects for more details about online informed consent). The web app will then randomize participants to one of the three arms. Finally, for participants assigned to the enhanced condition, the web app will walk participants through downloading the eTEST app from the Google Play or iTunes stores. Access to the eTEST app will be restricted to users registered in the eTEST web portal who are directed specifically from that site. Participants will also be encouraged to keep the app downloaded on their phone throughout the study period and will be encouraged to register any changes in their mailing address or smartphone

information (number, phone OS) as soon as possible, either through the eTEST app, web portal, or by notifying study staff.

Once users have registered, staff will conduct a brief introductory call with all participants to ensure that their information is correct and that they understand the study's requirements. After successfully completing this call, study staff will mark these participants as 'fully enrolled,' activating them in the study database. For **control** group participants, test messages will be sent to remind users when they are due to test. Tests will include a link to a web service listing nearby clinics offering HIV testing, as well as their location, phone number, hours, and cost. For **standard** HBST group participants, staff will send an HBST kit to their confirmed shipping addresses. These participants will receive no phone-based follow-up, but can use OraSure's provided 1-800 number for questions or needs. We will follow the same steps for **eTEST** participants, except that each test kit will be fit with an Estimote™ beacon. Beacons will automatically detect when each kit is opened and relay this information to a central study database, which triggers an email notification sent to counselors. Within 24 hours of opening the kit, an HIV test counselor will call eTEST participants to conduct post-test counseling and refer them to other needed services, including PrEP (see Section 3C.3.6.1.). HIV test counselors will be bachelor's-level staff who are certified as HIV test counselors and will have crisis intervention training. Clinical assessment and analysis of mental health will remain a responsibility of the licenses study clinician. At least one HIV test counselor will also be fluent in Spanish. Counselors will record data during each call in the study database. In each condition, participants will receive these interventions every three months over the course of the study period: at baseline, 3, 6, and 9 months.

Online surveys will use Qualtrics and will be hosted on Brown University servers. On each quarterly survey's due date, the study database will automatically send participants an email with language-specific instructions and links to the surveys. Participants will be asked to complete these within two days, and reminder emails will be sent every other day for seven days after the due date. If participants have not completed the survey within a week of their due date, site-specific RAs will contact participants by phone, text message, and email to encourage adherence. For all participants, those who fail to complete two consecutive quarterly assessments will be considered to have withdrawn from the study. After participants complete their final online survey, they will be asked to present to designated clinics for in-person HIV testing to finish the study. Site RAs will conduct follow-up calls with participants to ensure adherence to this procedure. Study payments will be issued via a reloadable debit card that will be mailed after participants are activated in the study. Participants will earn $25 for the baseline survey and each of the five quarterly surveys they complete, with a $50 bonus for completing all within a week of their assignment. They will also earn an additional $50 for completing the in-person HIV test after the study is finished, for a possible total of $250.

Focused information/counseling on PrEP. PrEP education and counseling will take place at each post-test phone call with participants in the eTEST condition. During the first call, HIV test counselors will provide a brief PrEP education session, covering indications for PrEP eligibility, a description of the medication used for PrEP, and an overview of common side effects and clinical follow-up (every three months). In our past work, we have employed an effective, five minute PrEP education session during in-person HIV testing that resulted in greater PrEP awareness among MSM131, and this will guide the education delivered during HIV test counselor phone contacts. Following the education content, participants will asked whether they are interested in making an appointment with a medical provider for PrEP consultation.

Interested participants will be provided with contact information for the local clinical sites where PrEP is provided. During subsequent phone calls, HIV counselors will re-assess PrEP interest and provide additional information upon request. Those indicating interest in PrEP at a prior call will be asked whether they made an appointment, initiated PrEP, and have attended follow-up appointments, which will be corroborated by reviewing medical records.

Design Considerations. We designed this study to approximate (as closely as possible) what the eTEST program might look if it were implemented in real-world settings, while also balancing the need to collect thorough and valid data on the program's effects over time. Given this, these procedures balance being as "hands off" as possible with conducting follow-ups that allow us to understand the program's effects thoroughly and accurately. This guided our decisions to (1) allow participants to consent and enroll remotely (2) use online surveys and (3) offer phone counseling to eTEST participants who test both positive *and* negative. First, while our pilot study required an in-person meeting for participants to enroll, the proposed research enables participants to provide consent and enroll remotely, because we believe one of HBST's key strengths is its potential to reach high-risk MSM who do not otherwise engage with traditional, "brick-and-mortar" services7-9. Thus, to reach these high-risk MSM, we believe it is important to allow them to test more regularly without the inconvenience and stigma of a face-to-face appointment. We realize that this may present
difficulties in terms of ensuring that participants are valid. However, to address this issue, multiple entries from the same IP or device will be blocked, and participants must verify their email addresses when registering, as well as other contact information via a call with staff after enrollment. Second, we chose to assess key self-report outcomes using quarterly online surveys to minimize participant burden, to minimize conditioning effects, and to allow a more accurate and "hands off" view of each conditions' effects. Since requiring in-person visits could artificially inflate adherence to key outcomes (e.g., HIV testing), we opted to use less burdensome online surveys. Third, the most important benefit of using the eTEST system is likely its ability to efficiently link those who test preliminary positive via HBST with confirmatory testing and care. As such, we considered several potential ways of providing phone follow-up with only these high-priority users (e.g., asking users to submit images of their test96). However, some authors have noted that another key limitation of HBST is the lack of follow-up and referral for other services (e.g., STI testing, PrEP) for those who test negative11; 12. We believe that arriving at best practices for *how* to offer post-test follow-up with HBST and *with whom* are key questions that are best addressed after its effects are first well understood among *all* participants. That is, we believe it is important to first understand whether offering follow-up in both of these scenarios confers an appreciable benefit beyond standard HBST. Finally, we also realize that requiring eligible participants to have a smartphone with a data plan or home wifi may exclude an important subset of MSM who may be at high risk for HIV, including those with financial difficulties or unstable housing132; 133. However, this criterion is consistent with our focus on MSM who use "hookup" apps. Of the 1,269 participants screened from Grindr for the pilot study, 97% reported having a smartphone with a data plan. Recent data also shows that 60-80% of unstably housed individuals, including minority youth, had smartphones with data plans134; 135. Nevertheless, this requirement is a limitation of this study. Future work should

address this limitation by exploring other ways of providing monitoring/ follow-up after HBST, such as text messaging or by providing low-cost devices to users.

Planned Analyses

Analyses will be conducted in Year 5. To evaluate Aim 1(a), we will use factorial logistic regression to test whether rates of having completed any HIV test over the 12 month study period (assessed via self-report and/or clinic records) differ by study condition. Condition, study site (and their interaction) and other relevant covariates will be entered as predictors, allowing us to explore whether each condition's effects differ by study site. To explore the effects of study condition on regular HIV testing, we will use a generalized estimating equation (GEE)136; 137 for repeated, binary outcomes, specifying whether participants tested during each 3-month study period as the focal outcome. A logit link function and independent correlation structure will be specified, with study condition, site, and relevant covariates as predictors, to test whether the odds of testing differ across time period, condition, and site. GEEs are a fitting approach for studies in which correlations between repeated measures variables are to be controlled, rather than a central focus of the analysis136; 137. For all models of **HIV testing** outcomes, a covariate reflecting whether a given participant had initiated PrEP (and when, for longitudinal models) will be added to each model, since these individuals are required to test for HIV quarterly as a part of ongoing PrEP care. Doing so will allow us to estimate the effects of study arm on HIV testing among those who did not initiate PrEP. Given that we have proposed collecting 54 more participants per site (162 total) than is required to estimate our most complex model (see Model 1b in Section 3C.3.10), we believe we will be fully powered to test this model, even with a high rate of PrEP adoption. While contamination of the control group in our pilot study was rare (only one control participant reported using a HBST), we will also track **where** each participant tested (at home, in person) in quarterly surveys. If contamination is significant, we will employ methods aimed at reducing this bias, including adding indicators of contamination as covariates or bootstrapping138; 139. To evaluate Aim 1(b), we will generate variables reflecting whether participants received testing for other STIs or risk reduction counseling during each of the four 3-month intervals of the study period. Similar GEE models will be estimated for these outcomes with time period, condition, and site as predictors, to test whether the odds of receiving each service differ across these factors. To evaluate Aim 2, we will code variables indicating whether participant reports or clinic records reflect participants having consulted with a medical provider about PrEP and/or received a PrEP prescription any time across the study period. Factorial logistic regression with study site, condition, and their interaction will be entered as predictors of this outcome, to test whether the odds of having received consultation and/or a PrEP prescription differ across each of the study sites and conditions. Overall, data from those who drop out or withdraw from the study will be used in these analyses, in intent-to-treat (ITT) fashion140. Similarly, we will assume values of zero for all outcomes (i.e., non-receipt of testing or services) when quarterly assessments are missing but participants are retained in the study. Depending on the degree of missing assessments, we will use multiple imputation for these values141, since data from missing assessments will likely be missing not at random.

Cost-effectiveness analyses (CEA). To examine the cost effectiveness of each condition under various scenarios (e.g., population prevalence/incidence, with/without follow-up for specific users, retesting intervals, purchase price), we will use mathematical models similar to those used in past CEA studies of HIV testing strategies142; 143. In CEA, a strategy is considered cost-

effective if the gains in health justify the resources needed to implement the program144; 145. The basic element of CEA is the incremental cost-effectiveness ratio, or the difference in the total costs associated with a given testing program versus an alternative, over the difference in incremental health improvement conferred by each program, generally measured in Quality Adjusted Life Years (QALYs)146. While HIV testing programs can lead to increased costs because treatment can begin earlier and continue for longer, these costs can be offset by lower rates of hospitalization and treatment for opportunistic infections, and more QALYs. To evaluate Aim 3, we will calculate the total annual costs associated with providing each HBST condition (standard and eTEST), including the costs of tests, postage, sensors, web development/maintenance, counselor resources, training, and supervision. Some of these costs depend on flexible aspects of the program, including the retesting interval (3 mos., 6 mos.), follow up strategy (only positive tests versus all tests) and purchase price. As such, we will estimate the marginal intervention costs under various scenarios to compare them with similar estimates for clinic-based, rapid HIV testing programs for MSM in high-prevalence areas from the literature142; 143; 147; 148. Potential health gains from testing programs include: Longer life, better quality of life, reduced risk of transmission to others among those with reactive results due to earlier awareness, diagnosis, and treatment entry, and reduced future infection risk among those testing negative by linking them with PrEP and other prevention services149-151. These also depend on outcomes for each program, like test acceptance, the number/timing of new cases detected, rates of linkage to care and treatment initiation, and rates of linkage to other prevention services among non-infected individuals. Gains conferred by these factors will be estimated using study data and available studies to compare them with existing programs125; 126. Overall, the goal of these simulations is to arrive at an estimate of the costs associated with each HBST program under various conditions per quality-adjusted life year (QALY) gained, so that they can be compared with similar estimates for clinic-based testing programs targeting similar populations. These estimates can then be used to evaluate whether providing low or no-cost HBST (with or without follow-up) can be cost effective when targeted toward certain high-incidence populations, compared with existing clinic-based approaches.

Exploratory analyses on new HIV cases and time to diagnosis. A key advantage of achieving more frequent testing through HBST could be the ability to detect more new infections and do so earlier, ideally before disease advances and others are infected. Given this, as exploratory aims, we will also examine whether more new cases are detected, and detected earlier on, using HBST compared to relying on clinic-based testing alone. To facilitate this, all participants will be tested in-person at the conclusion of the study, to ensure that HIV test results are available for most participants, even if they elected not to test using the study interventions. Among those who did not test during the study period, new cases detected through the post-study test will suggest that the interventions likely "missed" these cases. The proportion of cases detected with study interventions versus those missed can then be compared across conditions. Confirmatory testing in those who receive a reactive test at any time during the study, together with post-study testing for all participants, will also allow us to use CD4 counts and viral loads from positive blood tests to explore differences in estimated time to diagnosis among those infected during the study period, using methods described in past studies129; 152. These aims are secondary, however, since we acknowledge that there may be insufficient numbers of those infected with HIV during the study period in each group to conduct fully-powered tests. However, based on estimates of the rate of new infections among those without an HIV diagnosis in each study site's area74, we estimate that at least 20 participants (6 per group) may

be diagnosed with HIV during the study period. This will allow some limited exploration of these aims.

Power Considerations. We used past studies153; 154 and power estimation/ simulation packages in *R*, to determine the sample sizes necessary to detect significant effects in each of the models proposed in 3C.3.8. Relative risk ratios (RRs) were estimated for relevant outcomes (e.g., HIV testing, STI testing) across study conditions in our pilot data, and we used the smallest of these group differences for estimation so as to provide the most conservative estimate of required sample size. For each estimate, we assumed α=0.05, an observed power of .80, and a small but constant effect (1.2) for study site on each outcome, to ensure that any differences emerging between study sites could be detected. For GEE models, we assumed quarterly measurements (T = 4), with relatively independent relationships between repeated data (Φ=0.2). Table 2 summarizes the models, outcomes, parameters, and sample size estimates for each aim. For GEEs, sample size gives the estimated number of participants needed to test condition effects within each site. The sample
size required to detect the most complex model with the smallest effects is 246. To account for missing data, we propose collecting 300 MSM at each site.

B.5 Human Subjects Involvement, Characteristics, and Design

Participants will be 2000 males who are 18 years of age or older, not currently on PrEP and who have not received an HIV test in the last year. Focusing recruitment toward these individuals will allow us to examine whether the eTEST system and HBST increase testing and receipt of additional prevention services among those who rarely test and may be more difficult to reach with traditional prevention resources (i.e., clinic-based testing). Eligible participants will also report any of the following in the past 6 months: (1) anal sex (receptive or insertive) without condoms outside of a monogamous partnership with a recently tested, HIV-negative male, (2) having been diagnosed with an STI, or (3) having anal sex with an HIV-positive male. This criterion will ensure that the research is conducted among MSM who are at high risk for HIV and who meet DHHS criteria for pre-exposure prophylaxis. Since the research involves receiving HBST kits by mail, eligible participants will also be required to have a secure and stable residence to minimize the potential that tests may be stolen or diverted. This criterion was informed by past qualitative studies suggesting that most high-risk MSM prefer to receive tests by mail50; 51, as opposed to other delivery avenues (e.g., vending machine, pharmacy pickup). However, future research should address methods for providing “active” follow-up after HBSTs that are delivered via other routes, since many at highest risk may not have stable residences. Next, to be eligible, participants must currently have an Android or iOS smartphone with a data plan or a wifi internet connection at home. This ensures that the eTEST app can detect HBST kit openings when participants use the test at home. Finally, eligible participants will also be required to be fluent in either English or Spanish. All research materials will be translated into Spanish, and at least one test counselor and the LA site research assistant will be fluent in Spanish. These steps will ensure that we can explore the program’s effects specifically among Spanish-speaking Hispanic and Latino MSM. No special or vulnerable populations, as defined by 45 CFR Part 46 (e.g., prisoners, pregnant women, fetuses) are involved.

Participants will be recruited from each community (Providence, RI/Boston, MA; Los Angeles, CA; Jackson, MS) using ads placed on popular geolocation-based, gay-oriented mobile apps and sites (e.g., Grindr, Scruff, Jack’d). After clicking on the ad, interested participants will

then be taken to a mobile-optimized, interactive web application that will provide more information about the study, assess eligibility criteria, and document informed consent. Since participants will provide informed consent entirely online, we will ensure that the key study requirements are easily visible and presented in lay terms. Participants will also be required to enter their initials to indicate their consent to key parts, as well as the consent as a whole (see Section B.1. for more detail). After providing informed consent, the web app will then collect registration information from participants (e.g., name, phone number, email, address) before guiding them through a series of simple screens designed to orient them to the study. Randomization to a study condition will take place after participants complete the study consent, and this will determine which "on boarding" (orientation) sequence participants are shown. Participants assigned to the eTEST condition will be "funneled" toward downloading the eTEST app, while those assigned to Standard HBST and Control conditions will not be directed to the app store.

Once participants have completed this sequence, research staff will place a phone call to each participant within 24 hours to verify their contact information, ensure their understanding of the study requirements, and answer any questions about the study. Participants who do not complete this call within 72 hours of completing the orientation sequence will be considered 'not enrolled,' andthey will be considered as withdrawn from the study. Likewise, participants who do not recall basic information about the requirements of the study (e.g., that they are expected to complete quarterly surveys online, that they will receive letters or test kits in the mail every 3 months) will similarly be considered 'not enrolled' and deleted from study databases. All eTest participants will be instructed to keep the app downloaded as much as possible during their time on the study. Since the SQL database associated with the app allows us to track when users uninstall it, we will contact participants who delete the app by phone and email to inquire about their interest in continuing with the study. We will also track data on app uninstalls (e.g., reasons for uninstalling and/or withdrawing) to continue examining the usability and burden of the app. eTEST participants who change their smartphones during the study period (due to an upgrade, change in service provider, or the phone being lost or stolen) will be able to re-download and login to the eTEST app from app stores appropriate to their operating system (iOS, Android). Minimal study data is stored on participants' smartphones themselves; Instead, most data is stored on a centralized, secure database hosted on Brown University's dedicated servers. This data is password protected and can only be accessed by essential study staff members. All participants will also be allowed to update their personal information at any time, either through the eTEST native app (for eTEST participants) or through a study web portal (for standard HBST and control participants). Quarterly surveys will also inquire about any changes in participants' contact information (e.g., address, phone, email) each month.

As in our pilot study, to avoid influencing the study results, participants in HBST conditions (eTEST and standard HBST) will not be given explicit instructions about whether or not to use the tests sent to them (except during eTEST follow-up calls, which will encourage re-testing every 3 months). They will be informed that HBST kits will be sent to them 1 week, 3 months, 6 months, and 9 months after initially signing up, and that they can choose to take these tests or not. For eTEST participants who choose to take the tests, they will be informed that they should expect a call from an HIV test counselor within 24 hours of opening it, and that these calls are intended to provide post-test counseling, information about HIV prevention, and referrals. Push notifications on participants' smartphones will also notify participants at the time their test kits are opened that it was detected and that they should expect a call. Participants can

refuse any part of the discussions with counselors at any time. All participants will also be informed that, should they indicate having tested positive using an HBST through the quarterly surveys, a test counselor will follow up with them within 24 hours to ensure that they have made an appointment at a local clinic for confirmatory testing and care, if needed. If not, counselors will facilitate scheduling this appointment during their calls with these participants.
For eTEST participants that open their tests, counseling calls will be placed within 24 hours. These calls will be made by paraprofessional, Bachelor's level staff members who are employees of the Brown University School of Public Health, work in a "call center" physically located at Brown University, and who have been certified as 'Qualified HIV Test Counselors' in Rhode Island. This training ensures that candidates have basic knowledge of HIV and other sexually transmitted infections, understand HIV testing and how to conduct the test, and are familiar with counseling strategies needed to address many of the issues that commonly arise in those being tested. The training is conducted each year by Dr. Chan (Co-PI). Counselors will also receive training in triaging crisis intervention, which is provided by behavioral health staff at Lifespan. Clinical assessment and analysis of mental health will remain a responsibility of the licensed study clinician.

Additional study-specific training will involve principles of conducting phone-based counseling, role plays, and direct observation through recorded counseling sessions, as well as clinic-based testing conducted at Lifespan (supervised by Dr. Chan). Drs. Chan and Wray will also provide ongoing supervision to phone counselors throughout the study. Importantly, all follow-up calls will follow the CDC's guidelines for HIV counseling, testing, and referral155, and as such, will involve similar post-test counseling procedures that are currently provided by paraprofessionals and service providers in clinic- and community-based settings worldwide. Participants who test positive with HBST (those in either the standard HBST or eTEST conditions) will be assured that an initially reactive result is not a confirmed positive result. Counselors will then assist participants in scheduling an appointment for confirmatory testing with specific designated clinics at each study site (**Miriam STD/HIV Clinic** or **Fenway Health** in Boston, MA/Providence, RI; **OpenArms** in Jackson, MS; or **AHF Wellness Center** in Los Angles, CA) via three-way calling while participants are on the line. Each of these centers/clinics has standard procedures for providing newly diagnosed patients ongoing HIV care. Site PIs maintain professional affiliations with each, so that site-specific research staff can ensure/confirm whether each participant successfully made their appointments. Test counselors will conduct follow-up calls after each participant's scheduled appointments to ensure that they receive confirmatory testing. Participants with reactive test results will also be screened for suicidality during these calls, and if necessary, intervention will be provided according to National Suicide Prevention Lifeline procedures156; 157.
For each study metro area, "primary referral" sites have been designated that provide comprehensive HIV/STI prevention and care services. Each of these sites also provides HIV/STI testing services on a walk-in basis, for free. Study staff and counselors will recommend these clinics to participants first, particularly for confirmatory testing and care for any who receive reactive tests while on the study. These clinics will also serve as the primary site of referral for clinic-based tests they are to receive at the end of their study period.

Site PIs each have close connections with these clinics through their current clinical roles. Letters of Support have also been provided for each. However, each area also has several other options for HIV/STI testing, with locations that may be more convenient for some participants.

As such, a list of these clinics is provided through an HIV/STD test locator function of the app, and participants will be able to choose from these clinics, as well. Below is a list of primary sites (identified with *) and other HIV/STI testing sites, grouped by study metro:

Jackson, MS

- **Open Arms Wellness Center***; 805 East River Place, Jackson, MS 39216. (601)-500-7660. Walk-In Hours: Mon through Fri, 8:00 am to 5:00 pm. Cost: Free. *Dr. Mena serves as medical director at this facility.*
- Crossroads Clinic – Hinds County Health Department; 350 W. Woodrow Wilson Avenue, Suite 2516, Jackson, MS. (601)-987-6728. Hours: Mon through Fri, 8:00 am to 5:00 pm.
- Jackson Medical Mall – Hinds County Health Department; 350 W. Woodrow Wilson Drive, Suite 411, Jackson, MS. (601)-364-2666. Mon through Fri, 8:00 am to 5:00 pm.
- AIDS Healthcare Foundation**:** 766 Lakeland Dr #A, Jackson, MS 39216. Phone: (601) 368-3440. Wednesdays, 1:00 pm to 5:00 pm
- UMMC Adolescent and Young Adult Health Clinic: 350 W. Woodrow Wilson Avenue, Suite 459, Jackson, MS (601-815-3284) Mon, Tues and Fri, 8:00 am to 5:00 PM.
- UMMC Adult Specialty Care Clinic; 350 W. Woodrow Wilson Avenue, Suite 510, Jackson, MS (601-815-3120). Mon through Fri, 8:00 am to 5:00 pm

Los Angeles, CA

- **AHF Wellness Center***; 1300 N. Vermont Avenue, Los Angeles, CA. (866)-339-2525. Walk-In Hours: Mon, Wed, Thurs, & Fri, 5:30 pm to 8:30 pm; Sat 9:30 am to 4:30 pm. Cost: Free. *Dr. Klausner serves as Lab Director at this facility.*
- APLA Wellness Center – Beverly Hills; 3743 South La Brea Avenue, Los Angeles, CA. (323)-329-9900. Hours: Mon and Wed, 8:30 am to 5:00 pm.
- APLA Wellness Center – Long Beach; 1043 Elm Avenue, Suite 302, Long Beach, CA. (562)-432-7300. Hours: Tues, Thurs, & Fri, 8:30 am to 5:00 pm.
- Hollywood-Wilshire Public Health Center; 5205 Melrose Avenue, Los Angeles, CA. (323)-769-7932. Hours:
- Ruth-Temple Public Health Center; 3834 Western Avenue, Los Angeles, CA. (323)-730-3576. Hours: Mon, Tues, Wed, 7:30 am to 10:30 am & 12:00 pm to 3:30 pm; Thurs, 10:00 am to 12:30 pm & 2:00 pm to 5:00 pm. Fri, 7:30 am to 10:30 am.
- Los Angeles LGBT Center – Hollywood Jeffrey Goodman Clinic; 1625 N. Schrader Blvd., Los Angeles, CA. (323)-993-7500. Hours: Mon through Fri, 11:00 am to 7:00 pm.
- Los Angeles LGBT Center – West Hollywood; 8745 Santa Monica Blvd., 2nd Floor, West Hollywood, CA. (323)-993-7440. Hours: Mon through Fri, 11:00 am to 2:00 pm & 4:00 pm to 7:00 pm.

Providence, RI / Boston, MA

- **Miriam Hospital HIV/STD Clinic***; 1125 North Main Street, Providence, RI; (401)-781-0665. Walk-In Hours: Wed, Thurs, Fri, 12:30 pm to 3:30 pm. Cost: Free. *Dr. Chan serves as Director at this facility.*

- **Fenway Health – Ansin Building***; 1340 Boylston Street, Boston, MA; (617)-927-6000. Hours: Mon, Tues, 12:00 pm to 4:00 pm; Wed, 4:00 pm to 7:00 pm; Thurs, Fri by appointment. Cost: Free. *Dr. Chan and Dr. Wray have conducted past studies at this facility.*
- Rhode Island Free Clinic**;** 655 Broad Street, Providence, RI; (401)-274-6347; Hours: Mon, Wed, Fri, 8:00 am to 5:00 pm, Tues, Thurs, 8:00 am to 9:00 pm.
- Planned Parenthood – Rhode Island (low-cost); 111 Point Street, Providence, RI; (401)-421-9620. Hours: Call for appointment.
- Boston STD Clinic; 725 Albany Street, Suite 9C, Boston, MA. (617)-414-4081. Hours: Mon Tues, Thurs, Fri, 8:30 am to 4:00 pm; Wed, 8:30 am to 4:00 pm.
- Project Trust – Boston Medical Center; 721 Massachusetts Avenue, Boston, MA; (617)-414-4495. Hours: Mon through Fri, 9:00 am to 4:00 pm.
- Fenway Health – South End; 142 Berkeley Street, Boston, MA; (617)-247-7555. Hours: Call for appointment.
- Massachusetts General Hospital – STD Clinic; 55 Fruit Street, 5th Floor, Boston, MA; (617)-726-3236. Hours: Tues, Thurs, Fri, 8:30 am to 11 am; Wed, 1:00 pm to 3:00 pm.

Referrals will also be offered to local, LGBT-friendly agencies for substance abuse treatment, mental health treatment, and primary care, upon request. Lists of these clinics and services will be generated by site-specific study personnel (site PIs and RAs), updated as needed throughout the study, and will be provided to participants through the app, via text, and in every test kit package sent during the study.
All study procedures, including data collection, will be conducted by research staff, Co-PIs (Drs. Wray and Chan) or site-PIs and Co-Investigators (Drs. Klausner, Mena, Brock, and Needleman). Research staff will receive intensive training in all study procedures from Drs. Wray and Chan.

B.5.1 Sources of Materials Over the course of the study, data will be collected using the following methods:

1. Custom study web/mobile applications will be used to collect initial screening and registration data, mobile app user data, and sensor data. The web application will also be used by test counselors to log data from post-test counseling phone calls.
2. Online self-report questionnaires will be used to collect baseline and quarterly assessment data.
3. Audiotapes of post-test counseling phone calls will occasionally be recorded for the purposes of supervising test counselors.
4. Clinic records verifying service use will also be used to corroborate participants' reports about appointments attended, services, sought/conducted, and results/lab values from HIV/STI tests conducted.

B.5.1.1. Custom study web/mobile applications. Custom web and mobile applications have been developed specifically for this work with data safety and participant confidentiality in mind. Both elements have been used in this project's pilot phase (see Section 3A.5.), but will be further refined during the proposed project's start-up phase to meet the specific needs of this project. While the institutions involved in this research do not constitute 'covered entities' under HIPAA, guidance on data security issues provided through HIPAA/HITECH policies, workgroups, and

work statements provide useful guidance for ensuring the security of health-related data that is collected, stored, and transmitted using web-based tools. As such, we will ensure that all components are developed to comply with these requirements (including the HIPAA Security Rule) for electronic protected health information and other health data158. The web and mobile applications will be part of a complex web-based architecture in which all staging components (onboarding web app, participant-side web portal, administrator portal, and mobile app) interact with a centrally-hosted database. The web application will be used to collect self-report and registration data during the screening process (contact, login information). Registration data (current contact information and preferences) can be updated by participants at any time throughout the study by logging in to the secure web portal or the mobile app (for eTEST condition participants). An admin panel of the web application will also be used by study test counselors to log data from post-test counseling phone calls, including testing date, time, and results, referral information provided. The mobile application will be used to collect and relay sensor and device data, user preferences, to provide interactive information about prevention services (e.g., HIV testing, HBST, STI testing, safe sex, PrEP). Both applications are currently hosted locally (on Brown University's servers), ensuring that they are protected by Brown's strict security policies. These policies include server-specific firewalls, restricted access through a virtual private network, IP-specific verification, and encryption (both at rest and in transit). These servers are maintained by IT staff that also provide regular, secure backups, and control physical access via badge entry and sign-in with video surveillance. Together, these specifications ensure that only essential research staff have access to the data that are collected and stored by these tools.

B.5.1.2. Online self-report questionnaires. Online questionnaires will be used to collect self-report data as part of the baseline and quarterly follow-up assessments. These questionnaires will be developed and hosted using Qualtrics, which is a web application that affords custom development of web-based surveys. Qualtrics allows strict password protection and limited survey access which ensures that only essential research personnel at the study site will have access to the study data. For these reasons and others, Qualtrics can be used to collect many types of sensitive data, including 21 CFR Part 11, FISMA, and HIPAA data. Surveys can also be mobile-optimized within Qualtrics, allowing study participants to complete surveys on a variety of devices. Qualtrics is currently used by our research team.

B.5.1.3. Audiotapes of post-test counseling phone calls. Phone calls between test counselors and eTEST condition participants will occasionally be recorded for the purposes of conducting supervision with test counselors. These tapes will be collected using electronic recording equipment and will be stored in digital files on Brown University's servers. However, they will be stored only until the next supervision meeting (weekly) and will be deleted immediately afterward.

B.5.1.4. Clinic records verifying service use. We will also review the records of area clinics to compare with self-report data for each of the proposed outcomes (e.g., HIV testing, STI testing, PrEP consultation, receipt of a PrEP prescription). To facilitate this, participants will be asked to sign and return a HIPAA release in the case that they tested outside of the site clinics. The study informed consent process will also specifically ask participants to consent to allowing us to release limited personal information that reveals their participation in the study to the clinics they

identify for the purposes of verifying service receipt and collecting limited clinical data (e.g., HIV/STI test results, and if positive, CD4 counts and viral loads). Quarterly online surveys will ask participants to name the specific clinics where they received each of the services that the questionnaires inquire about, and site-specific RAs will then request records from these clinics for these participants. Site-specific RAs will download participant data to explore service utilization and compile lists of participants who noted receiving services at each clinic. RAs will then contact each clinic that a participant utilized for HIV/STD testing. Once clinic data is received, site-specific RAs will code it using participants' unique study ID numbers and store it in password-protected files on Brown University's secure servers.

We realize that not all services will be verifiable (e.g., anonymous HIV testing), and that some participants may not be comfortable signing broad releases for their medical information. We also acknowledge that requiring the release of personal medical data may serve as a barrier to enrolling for some participants. At the same time, we also believe it is important to collect more objective data that can serve as a compliment to self-report whenever possible. Given these considerations, returning a signed release will not be required in order to enroll in the study, to prevent this procedure from acting as an impediment to enrollment. Instead, we will verify clinical service information for those who return their releases and consent to this specific procedure. This approach will allow us to verify as much clinical service data as possible, while minimizing participant discomfort with the study's procedures. While this likely means that data on clinical service use will be incomplete, we do not believe that incorporating this procedure undermines the importance of self-report data or the study as a whole. (See Section B4 for a full list of data collected from clinics.)

*Data Use Agreements will be put in place to allow staff at each study site access to the study database (saved on Brown's servers) in order to verify service use and enter data collected.

C. Risks to Participants and Procedures to Protect Against Risk

C.1 Adequacy of Protections against Risk

We will make every attempt to minimize risks to participants throughout the study protocol, including loss of confidentiality or privacy and psychological discomfort.

C.1.1 Recruitment and Informed Consent Procedures

Recruitment. All participants will be recruited via geographically focused advertisements placed on MSM-oriented "hookup" mobile applications (e.g., Grindr, Scruff). These advertisements appear as 'pop-ups' within the apps when users log in within a specified radius of a given metro area. If users click on a 'More Info' button within these ads, they are directed to a 'landing page' for the eTEST study, which represents the first portion of the web app's user-side onboarding process. After selecting their desired language (English/Spanish), a sequence of screens will explain the study in very simple terms. Then, basic eligibility criteria will be assessed using a series of online forms (see Section 3.C.3.4.). "Ballot stuffing" prevention

measures will be deployed to ensure that participants do not complete the eligibility assessment multiple times (e.g., barring multiple entries from the same IP or device MAC address). Eligibility data will be discarded if participants do not meet criteria, and an error message will display notifying users that they are not eligible. Those who are eligible based on this data will be directed to create a user account in the web app before being directed to informed consent screens.

Informed Consent. On the first informed consent screen, participants will be able to elect to either read (written), hear (audio), or watch (video) a plain-language explanation of all information included in the consent process. Consent information will be explained/written at a sixth-grade reading level and important concepts will be highlighted via bulleted text, highlighted text, and/or captions. Participants will be required to type their initials next to each key concept presented to ensure that they have seen and understand each, as well as to indicate their overall consent. A short, three question 'quiz' will assess whether participants understand what is being asked of them. Those that get less than three correct will be returned to complete the informed consent section again. Those who enter correct answers to these questions will move on to complete the study baseline questionnaire. Afterward, those assigned to the eTEST condition will be directed to download the app from the app store specific to their OS (i.e., Android/iPhone).

Research staff and study test counselors will receive notifications, both via the administrator-side of the web app and via email, that a participant has completed their "onboarding" sequence. Staff will then conduct an introductory call with each participant. This call is designed to further emphasize the key points made by during the informed consent process, verbally assess participants' understanding of the concepts, confirm contact information, and to stress the importance of adherence to the study. These calls will last approximately 10 minutes. Based on this conversation, if staff/counselors have reason to believe that a participant is not aware of study requirements and/or may be unable to provide informed consent, he/she will notify the participant that they are ineligible. If staff/counselors believe the participant understands and can provide consent, they will be formally considered "enrolled" after all other information is checked and verified.

Payments. Participants will be compensated on the basis on their completion of quarterly assessments, as well as the follow-up appointment conducted at the study's end. They will earn $25 for the baseline survey and each of the five quarterly assessments they complete, with a $50 bonus for completing all assigned surveys within a week of their assignment. They will also earn an additional $50 for completing the in-person HIV test after the study is finished, for a total of $250. Participants will be paid for each survey immediately after completing it using a reloadable debit card that will be sent to each participant after enrolling. Study payments will be managed using the shared study database and issued by staff at Brown University. We successfully used this system, as well as a similar compensation schedule, in our pilot study (see Section 3.A.5.). Compensation amounts are consistent with payments provided for research participation at Brown and other institutions, thus posing little risk of coercion.

C.2 Procedures to Protect Against Risk

C.2.1. Protections against the loss of data security, confidentiality, and privacy. Before beginning their work on the study, all members of the research staff will receive thorough training in procedures designed to maintain data security. Informed consent procedures have been specifically designed to ensure that participants are aware of the study's potential risks to confidentiality and privacy. We have elected to conduct this consent process entirely online, because we believe that the eTEST system may be most appealing and beneficial for those MSM who may have been deterred from testing because of the face-to-face interaction that is normally required. However, the online informed consent process is thorough, and involves several steps designed to ensure that participants understand its key components, including: presenting key concepts in several formats (written, audio, video), condensing presented material to key points, requiring that participants initial each key point, and requiring that participants complete a short quiz to demonstrate their understanding. RAs will also call participants on the phone to verify their understanding of study procedures before considering them 'enrolled.' While some may have reservations about conducting and collecting informed consent online, we believe doing so offers participants a better opportunity to consider their participation in private and freely decline participation, if they so choose. We also believe that these steps for ensuring participants' informed consent also actually exceed of those undertaken in many in-person consent procedures.

(1) Data security. While collecting and storing participants' personal information using web-connected databases is unavoidable due to the nature of the study, a number of steps will be used to help secure and safeguard this data throughout the project. All elements of the proposed web architecture (web application, mobile application, database) will be hosted on Brown University's secure internal servers. Hosting these elements locally has the benefit of allowing us to enforce a strict set of security and authentication rules and exercise more control over who has access to the data (i.e., to only essential research staff, and information technology staff directly involved in maintenance and oversight of the server). We can also require additional security measures for all authorized individuals, such as two-step verification (a password plus registered device), VPN-only access, and IP-specific firewall rules. Access to participant information will be restricted to essential research staff, and only after two-step verification. Given the sensitivity of some of the data collected as part of this project, servers running elements of the eTEST architecture will conform to 'restricted-level' server settings. In addition to more stringent virtual access controls, this designation also means more stringent physical access controls, and that Brown's Computing and Information Services (CIS) staff performs continuous monitoring, emergency support/backup, and regular penetration tests. More details about server security designations at Brown is available at: http://brown.edu/go/serversecurity.

Questionnaire data collected throughout the study will also adhere to similar server/data security measures, since these elements are also hosted on the same internal servers. Specifically, these surveys will be developed and hosted using Qualtrics, which allows researchers to create individualized surveys and host them on local servers, to ensure local control over security settings and access policies. By using Qualtrics, we can send online surveys to research participants that they complete on web applications hosted at Brown. These surveys can also be mobile-optimized, so that participants can easily complete them on their mobile devices.

(2) Privacy when using mobile/online tools and assessments. Since participants will complete quarterly questionnaires online, and some questions asked will be sensitive, they will be specifically instructed to complete these in a private location when possible. Emails that are automatically sent to participants to remind them to complete the surveys will also remind them

to complete assessments in private. Reminder emails will also contain no identifying information (other than their email address) or references to HIV testing or other sensitive topics.
All participants will have access to information about HIV and other sexually transmitted infections, testing, prevention, and referral information via the eTEST app. As such, they will be instructed to use their phone's lock screen to prevent unauthorized access. They will also be instructed to access this information only in private locations. Users will receive push notifications from the app, either to inform them that they are due for their next test, or to inform them about the status of their next HBST kit (i.e., that it has been shipped, that it has been opened and a counselor will be reaching out soon). These notifications will be worded as innocuously as possible (e.g., "Looks like you opened your test!"), and test opening notifications in particular only register when the device is in close proximity to the beacon (≈50m), ensuring that they display only when participants are already in a location in which they are comfortable taking the HIV test. Still participants will be encouraged to use their devices' native security settings (e.g., enabling a lock screen with code in order to access the phone) while they are in the study. No participants have expressed concerns about the privacy of the app in our pilot study. The Bluetooth low energy (BLE) beacons used in test kits do not collect or store any data. They only transmit information about the beacon and its state to nearby Bluetooth devices (e.g., smartphones).
(3) HBST Packaging. If participants have been assigned to either the standard HBST or eTEST conditions, OraSure OraQuick® HBST kits will be sent to the verified physical addresses of participants throughout the study. To safeguard participant confidentiality, these packages will be sent with generic return addresses (i.e., Brown University) and in discrete packaging. An information card will also provide participants with tips for ensuring their privacy while taking the test at home and for disposing of the test collection swab. OraSure provides an envelope container that participants can use to confidentially dispose of the test collection swab after the test is complete.
(4) Phone counseling/follow-up interviews. When conducting follow-up phone calls, counselors will first ensure that participants have adequate privacy to discuss the test over the phone, and if not, calls will be re-scheduled. Data from these calls will be manually entered by counselors into the study's central, password-protected database. Occasionally, counseling phone calls will also be digitally recorded for training, supervision, and fidelity purposes. These recording files will be password-protected and stored on Brown University's secure servers, in locations separate from participants' identifying data. Digital audio recordings collected for supervision purposes will be deleted immediately after supervision meetings have occurred. Those used for training and fidelity will be stripped of any identifying information that may have been recorded, and deleted after they have been used for these purposes.
C.2.2. Protections against psychological discomfort/distress. Several measures will also be employed to minimize psychological discomfort or distress as a result of the research. First, while participants may experience some nervousness or anxiety while taking an HIV test at home, past research suggests that this risk is low 159-161, and OraSure's clinical trial data suggests that HBST can be completed safely and with minimal distress. Nevertheless, participants in either HBST condition (standard HBST, eTEST) will be encouraged to report any distress they experience as a result of testing to study staff, who will provide referral to LGBT-friendly treatment providers in the local area. Second, some participants may receive "reactive" results during the study, so this possibility will be addressed during their "onboarding" and consent process. This sequence will explicitly encourage participants to interpret HBST test

results as “reactive” (rather that “positive”), since false-positive results are possible and further testing is needed to confirm “positive” results. Participants in any condition will also be encouraged to report receiving “reactive” results to study counselors as soon as possible, and will be provided with contact information for doing so. When reporting a “reactive” result, study test counselors will aid these participants in scheduling an appointment for confirmatory testing at clinics specific to their areas and at which site PIs have existing relationships (see Section A.2. for a list of these and other referral sites). Each of these clinics have established procedures for conducting follow-up testing and engaging these patients in ongoing HIV care. Finally, the risk of distress or discomfort from study assessments is low, but participants will again be encouraged to report this to study staff as soon as possible. Staff will then provide referrals to local MSM-friendly treatment resources and/or emergency services. In addition, research staff will be trained in responding to adverse events, including participant distress. These events will be reported promptly to the Brown University IRB and the IRBs of the relevant site. Together, we believe that these procedures greatly reduce any risks associated with the research, both in terms of data security and possible emotional discomfort/distress.