Stand Alone Protocol: mLab App – IRB-AAAR8760

mLab App for Improving Uptake of Rapid HIV Self-testing and Linking Youth to Care

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PI: Dr. Rebecca Schnall

Abstract:
The number of youth living with HIV continues to rise, and they are disproportionately represented at each stage of the care continuum. Most relevant to this application, it is estimated that less than half of HIV-infected youth in the United States (US) have been diagnosed with HIV, and AIDS-related deaths among youth have increased over the past decade despite decreased death rates among all other age groups, pointing to the urgent need for increased testing among youth. Black and Latino youth are at increased risk of poor HIV-related outcomes and have disparate testing rates as compared to White youth. Mobile Health (mHealth) technology is a powerful and relevant tool which represents a promising approach for improving outcomes among youth living with HIV. Youth are avid adopters and heavy users of smartphones and digital technologies, and these technologies offer opportunities to tailor interventions to developmental stages and personal needs. Importantly, these technologies are capable of delivering interventions in real-time and in ecologic settings. This creates an opportunity to remotely reach youth through mobile and connected health approaches to strengthen their HIV care continuum engagement and treatment outcomes. In response, our study team has developed the mLab App, an innovative mobile and connected technology that combines HIV prevention information with push notifications/reminders to complete HIV testing and an automated image processing feature to provide accessible, objective, secure, and real-time feedback on home-based OraQuick (lateral flow assay) HIV test results. The mLab App also contains an innovative automated data collection and a results reporting feature. Findings from our preliminary work in New York City indicate that youth perceive the mLab App as useful, easy to use, and effective at improving health outcomes and intend to use the technology. Findings from our preliminary work in Africa support the sensitivity and specificity of the imaging algorithm for interpreting lateral flow assay results. Theoretically-guided by the Health Information Technology Usability Evaluation Model (Health-ITUEM), the proposed project will refine and test a next-generation diagnostic intervention delivered on a mobile platform to improve HIV testing and linkage-to-care outcomes among youth living with and at-risk for HIV. Well in line with the objectives of RFA-MH-18-606, we will conduct a careful, iterative process of technology refinement based on input from end users, experts, and our youth advisory board. We will then enroll 525 high-risk youth (age 18-29 years) in a 12-month RCT to assess differences in HIV testing rates and linkage to care between arm1-intervention (mLab App), arm 2- Standard of care-HIV information control arm, and arm 3-HIV home test only. Finally, we will analyze paradata, defined as auxiliary data that capture details about the *process* of interaction with the technology, to understand the effect of user engagement of the mLab App on improving HIV testing rates and linkage to care. Interventions delivered through mHealth technology represent a promising approach for improving outcomes among youth. Given the pervasiveness, low cost, and convenience of mobile technology, the mLab App holds promise to help achieve the goals of the National HIV/AIDS Strategy in the US by increasing the number of persons living with HIV who know their serostatus, decreasing HIV-related disparities, and ultimately reducing the risk of HIV transmission and acquisition.

Study Aims:

The number of youth living with HIV in the United States (US) continues to rise, and the epidemic is exacerbated in racial, ethnic, and sexual minority youth who bear a disproportionate burden of the HIV epidemic. Estimates of ~ 80% of new infections occur in young men who have sex with men (YMSM) and young transgender women (YTGW), and the epidemic is further magnified in Black and Latino youth.[1-11] There are large disparities in HIV testing rates in youth and more specifically in our target study population, Latino and Black YMSM and YTGW. The low uptake of HIV testing in youth can be explained by a number of factors. Developmentally, youth often perceive themselves to be at low-risk for acquiring HIV as well as having an inaccurate perception of its impact.[12] There are also social and healthcare system factors that make YMSM and YTGW more vulnerable to becoming infected with HIV and less likely to be tested for HIV. Social factors include stigma, homophobia, and racism. These factors may cause YMSM and YTGW to feel rejected and isolated,[9, 12-15] and as a result they may not disclose their sexual orientation or gender identities[16] or seek HIV prevention and testing services.[12] Healthcare system factors include limited and inadequate access to youth-centered HIV testing services.[9, 17] As a result, many YMSM and YTGW do not seek HIV testing services and are therefore less likely to be aware that they are infected.[9, 11, 16, 18] HIV+ youth who do not know they are infected are not engaged in lifesaving treatment and care and are at risk of infecting others,[9] pointing to the urgent need for interventions to increase the uptake of HIV testing in Black and Latino YMSM and YTGW. Mobile health (mHealth) technology is a powerful platform for the delivery of HIV prevention interventions, including HIV testing,[19, 20] and is especially relevant for racial and ethnic minority youth.[21] Approaches using mHealth have the advantage of a simple interface for users, accessibility anywhere cell signals/Wi-Fi are available, relative affordability, and have been successfully promoted to reach stigmatized and disenfranchised populations.[22, 23] While preliminary evidence suggests that mHealth technology (e.g., smartphone apps) is feasible, attractive, and effective for promoting HIV prevention and care outcomes among youth, many apps have not been designed by end-users and, of those that do exist in the marketplace, none have not been well-evaluated with YMSM or YTGW.[24] Furthermore, the need is even greater in Black and Latino YMSM and YTGW, due to socioeconomic factors, cultural norms, stigma, homophobia, and discrimination.[25-34] Building on our extensive preliminary work,[35, 36] our multi-disciplinary team (public health scientists, clinicians, and engineers) has developed the mLab App, an innovative mobile and connected technology that combines HIV prevention information with push notifications for testing, a mobile phone imaging feature of a lateral flow assay (the OraQuick rapid home HIV self-test), and automated image processing to provide accessible, objective, secure, and real-time feedback on HIV test results. The mLab App also contains an automated data collection and results reporting feature, which relays test results back to the research team, and the study participant triggering messages to encourage future repeat testing for a non-reactive test or linkage to confirmatory testing and treatment for a reactive test. Our preliminary work in Africa supports the specificity and sensitivity of the image processing algorithm compared to visual interpretation of lateral flow tests[37] and has been successfully used with lateral flow assays for malaria testing in non-clinical settings. Preliminary work in New York City (NYC) indicates strong acceptability and feasibility of the mLab App in YMSM and YTGW.[38] Given our robust preliminary data, the innovativeness of the mLab App, and the public health need for the development of efficacious interventions to increase the uptake of HIV testing and linkage to care among high-risk youth, our study aims are to:

Aim 1: Refine the user interface of the mLab App – a mobile and connected health intervention for increasing the uptake of rapid home HIV self-testing (OraQuick) and linkage to care – by employing rapid cycle iterative design methods with feedback from human computer interaction experts (N=5), end-users (N=20), and youth advisory board members (N=10).

Aim 2: Evaluate the efficacy of the mLab App in improving both HIV testing rates and linkage to care versus standard preventive care in 525 Black, Latino and other young men and transgender women (inclusive of YMSM and YTGW age 18-29 years) in a 12-month multi-site trial, with randomization to three groups (intervention, standard of care-HIV information control arm, HIV home tests) at each site.

Hypothesis 1. Youth randomized to the **mLab App** *arm (arm 1), as compared to youth in the standard of care HIV information control arm, will have: a) increased rates of HIV testing within the first 6 months of the trial; and b) increased rates of re-testing in months 7-12 of the trial.*

*Hypothesis 2. The total number of youth who test HIV positive and link to care in the **mLab App** arm will be greater as compared to the standard of care HIV information control arm.*
Hypothesis 3. The image processing in the mLab App will: 1) have no statistically significant difference in sensitivity or specificity when compared to confirmatory testing, 2) have greater sensitivity and specificity when compared to the user-submitted self-analyses.
Aim 3: Monitor and analyze paradata to understand the effect of user engagement of the mLab App on improving HIV testing rates and linkage to care.
Impact: The proposed study addresses significant scientific questions and public health concerns through a rigorous and systematic effort to refine and test the mLab App intervention and better understand its most useful components to promote HIV testing and linkage to care among Black, Latino and other YMSM and YTGW – those most at risk for acquiring HIV but also the least likely to have been tested. Given the novelty and promise of next generation mHealth diagnostics and the high rates of undiagnosed HIV in youth (specifically YMSM and YTGW), the mLab App has the potential to significantly curb the HIV epidemic by improving detection and enabling youth to promptly seek confirmatory testing and follow-up care.[39] Building on our earlier user-centered design work,[24, 40] and integrating a real-time diagnostic device, this work has the potential to improve outcomes across the HIV care continuum for high-risk youth.

Background.
The number of youth living with HIV continues to rise, and they are disproportionately represented at each stage of the care continuum. Most relevant to this application, it is estimated that less than half of HIV-infected youth in the US have been diagnosed with HIV, and AIDS-related deaths among youth have increased over the past decade despite decreased death rates among all other age groups. *Simply stated – youth unaware they are HIV+ cannot get the treatment they need to stay healthy and may infect others without knowing it.* Thus, increasing access to HIV testing is a critical component to engaging and identifying YMSM and YTGW with undiagnosed HIV, linking them to care, and lowering forward HIV transmission.[20, 6, 8, 41-46]
YMSM and YTGW, and specifically Blacks and Latinos, are disproportionately infected with HIV. To illustrate, in 2015, youth comprised 22% of all new cases of HIV.[9] Of these youth, 81% of infections occurred among YMSM.[9] Among YTGW under the age of 29, limited data exists, but community-based samples suggest an HIV prevalence from 5% to 20% in this population.[47] These numbers are exacerbated in racial/ethnic minorities. Black men who have sex with men (MSM) have more HIV diagnoses than any other racial/ethnic group of MSM (38%) and Black YMSM comprise 39% of these HIV diagnoses.[7] Latino MSM comprise 27% of HIV diagnoses among MSM[7] and 7 out of 10 new HIV diagnoses among Latinos.[48] YTGW have also been disproportionately affected by HIV[10] with the highest percentage of HIV+ test results of any gender category.[11]
There are a number of behavioral and social factors that likely account for the high rates of new and undiagnosed HIV infections among youth, and specifically YMSM and YTGW. Engaging in receptive anal intercourse[49] and a higher likelihood of having partners who may be are at increased risk for HIV are some of the behavioral factors that potentiate the HIV epidemic in youth.[50-53] Moreover, having never witnessed the devastating effect of HIV/AIDS in the early years of the epidemic, youth may perceive themselves to be at lower risk of HIV.[12, 54] Social factors including stigma, homophobia, and racism may compound those factors; many YMSM and YTGW feel rejected, isolated, and/or lack social support.[9, 12-15] Healthcare system factors also contribute to the low HIV testing rates in youth. Many youth avoid contact with providers who offer HIV testing and care due to lack of health insurance,[55] discomfort with facilities and services,[56] fear of stigmatization,[57] and concerns about confidentiality.[58, 59] For these reasons, many YMSM and YTGW avoid HIV testing services,[10, 12] making them unaware that they may be infected with HIV.[9, 16, 18]
Outreach is needed among YMSM and YTGW to engage them in HIV testing, which remains an important tool in the fight against HIV.[60, 61] There are large disparities in HIV testing rates in youth and ethnic and racial minorities. Among those HIV-infected, only 49% of YMSM aged 18-24 years compared to 66% of adults[62] knew of their infection, highlighting the need for improved outreach for testing among high-risk youth.[19,27] Among all MSM, 54% of Black/African American men knew of their infection, compared with 63% of Hispanic/Latino men and 86% of white men.[5, 54, 63] – reflecting huge racial and ethnic disparities and the need for our proposed study that targets enrollment of toward Black and Latino YMSM and YTGW (NIMHD priority area).[45, 64, 65] Transgender women (TGW) of all ages are also immensely burdened by HIV. In one

study, TGW were shown to have a lower prevalence of ever having been tested (35.6%) or having been tested in the past year (10.0%) for HIV compared to cisgender gay and bisexual men (61.8% ever tested; 21.6% tested in past year).[11] TGW have consistently low HIV testing rates[66] and a resultant high percentage of undiagnosed infection in comparison to the general population,[67] pointing to the need for interventions to increase the uptake of HIV testing in this population.[68] YMSM and YTGW do not have adequate access to HIV prevention and testing [9, 17] and they have poorer access to healthcare, in general[12]. For example, Koblin (DSMB member) and colleagues found that Black MSM in particular were less likely to have a usual place for healthcare or to have visited a healthcare provider recently[69], thus providing scientific premise for the need to provide easier access to HIV testing services for this most at-risk group. The healthcare system is failing to test youth, contributing to the high percentage of youth with undiagnosed HIV; this is especially true for YMSM and YTGW who are often overlooked by the current healthcare system.[70, 71] As a result, more Black and Latino men end up being tested in non-clinical settings than White men,[72] pointing to the need for expanding non-clinical options, such as self-testing, especially among racial and ethnic minorities.[71, 73]

Scientific Premise to Support the Use of HIV Self-Testing. Concerns about the HIV self-test have focused on its potential to reduce contact with care providers or in healthcare settings where more sensitive tests may be warranted and other prevention approaches, such as pre-exposure and post-exposure prophylaxis, might be delivered.[74] Another concern frequently cited about the HIV self-test is that individuals who receive a reactive or preliminary positive test result may be less likely to seek or to receive a confirmatory test and be linked to appropriate care. Findings from a recent RCT suggests that when supported through a helpline, individuals identified as HIV+ through self-testing were adequately and appropriately linked to care.[75] Perhaps most importantly, there were no serious adverse events described in this study or in other HIV self-testing studies.[76] While HIV self-testing kits can be purchased over the counter, we acknowledge that there has been low uptake of HIV self-testing among YMSM in the US,[77] pointing to the need for technologies, such as the one proposed in this study, to promote the uptake of the HIV self-test (OraQuick). To our knowledge, no prior studies have looked at uptake among YTGW. Barriers are not only limited to cost; our research indicates that there is an overall lack of understanding of how to use the test correctly.[78] To overcome these challenges, we will use careful iterative feedback from youth and experts to refine the mLab App, a mobile and connected technology to improve HIV testing, diagnosis, and linkage to care. Mobile Health (mHealth) technology is a powerful platform for the delivery of HIV prevention strategies, including HIV testing.[19, 20] There is already extremely high mobile phone penetration in the US,[79] especially among racial and ethnic minority groups[21] and youth.[21] This creates the opportunity for health interventions in a portable format with enhanced privacy. mHealth is a powerful and relevant tool which can be developed to meet the needs of its end-users and has great potential to transform how healthcare is provided and consumed.[80, 81]

In response to the need for interventions to increase HIV testing in youth and in direct response to RFA-MH-18-606, our study team developed the mLab App, which affords advantages over existing self-test options to support the potential for higher uptake of the HIV self-test. The mLab App is a mobile app on your phone that is accessible using a login name and password. The app will provide HIV prevention information, push notification reminders for testing, step-by-step instructions for using the OraQuick HIV tests, an image upload function so you can send an image of your OraQuick HIV test to the study team. You will enter the results of the OraQuick test in the app. By

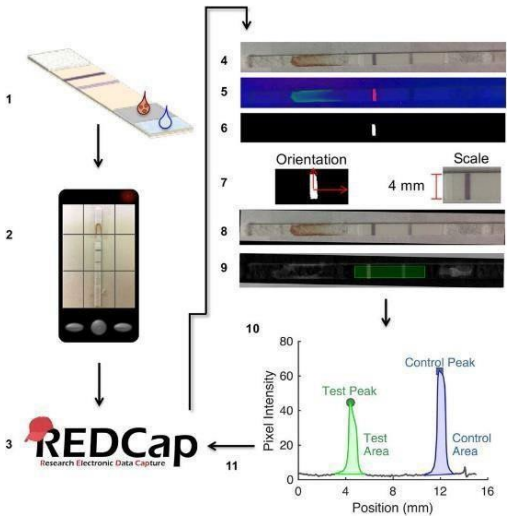

Figure 1. Diagnostic Strategy workflow and image-processing algorithm

using the app, we are asking you to help test the app's ability to interpret the

results of the OraQuick tests. You will not be able see the results of this interpretation. If you test HIV positive by the OraQuick HIV test, the mLab app will provide information on how to set up follow-up confirmatory testing within the following 24 hours. All information that you provide within the app will be stored on a secured server.

The mLab App is derived from extensive participatory based research (focus groups, design sessions, usability testing) with young men (CDC U01 PS003715) (described in detail in APPROACH: preliminary study #1).[35, 82] Building on this extensive user-centered design work and the engineering work of Dr. Scherr (Co-I; see APPROACH: preliminary study #3), who developed the automated image processing algorithm (Figure 1) to provide real-time interpretation of smartphone camera images of a lateral flow assays for malaria.[37] The mLab App extends the algorithm to interpret the HIV self-test (OraQuick).

The workflow of the app is provided as a powerpoint attachment entitled "20180912_IDE [redacted]_R8760_Schnall_mLab Workflow_Updated Octob."

The mLab App addresses many of the current barriers to self-testing kits through the integration with a smartphone to overcome ambiguous test interpretations, provide immediate results reporting, and help support linkage to care. In addition, the mLab user interface promotes a holistic diagnostic experience because it provides step by step error-checking with clear picture directions. While in principle, rapid tests, such as the OraQuick, seem simple to interpret[83] with weak positive bands or weak control lines, it is all-too-often difficult for users to accurately interpret the test results, which we found in our own research on the OraQuick home test.[84] Beyond diagnosis, the mLab App provides information facilitating linkage to care for those who test HIV-positive and educates users on the importance of follow-up testing and prevention services for those who test HIV-negative.

Paradata, defined as auxiliary data that capture details about the *process* of interaction with the technology, will drive our understanding of user engagement with the mLab App and of subsequent behavior change. Outcomes from HIV prevention and care studies delivered via a mHealth platform have primarily relied on analyses by group assignment and assume that participants' engagement is equitable within the intervention arm and stable for the duration of the trial. The use of paradata in technology interventions involving HIV prevention and care is an understudied area of interest.[85] While a number of technology-based HIV interventions have previously suggested that online behavioral interventions are acceptable and efficacious in promoting behavioral change,[86] a recent review of this literature identified very limited reports of participant engagement, measured through paradata, with a technology-based intervention.[87] In our own recently published work on the effect of a mHealth app for improving symptom burden in PLWH, we monitored app usage throughout the trial and reported this as part of the final outcomes of our study.[88] Given our prior work, we will examine paradata since this provides an opportunity to monitor and analyze aspects of the mLab App that may play a role in changes in HIV testing rates and linkage to care. By monitoring and analyzing paradata, components of the mLab App, such as the timing, location, and frequency of the rapid images of HIV tests taken by a user and access to other prevention information, will be instrumental in understanding what components of the intervention mediate behavior change. Engagement with the mLab App will furnish a greater understanding of user satisfaction and retention of our intervention. mLab App paradata will have implications for the scale-up and dissemination of this intervention as well as for the development of future technology-based HIV interventions with targeted behavioral outcomes.

Theoretical Framework. This study is guided by the Health Information Technology Usability Evaluation Model (Health-ITUEM), a technology acceptance theoretical framework that guides usability evaluations for assessing mHealth technologies.[89] This technology acceptance model was developed in response to the current gaps in the extant usability literature[90] and was validated by Schnall et al. for use with mHealth technology and has been widely used (cited 89 times since 2013). The Health-ITUEM integrates multiple concepts of usability from the Technology Acceptance Model[91] and the International Organization for Standardization standard 9241-11.[92] Guided by this model, we will carefully and iteratively refine the mLab App to ensure that the content and approach are engaging and usable since the two underlying tenets of technology acceptance are usefulness and ease of use.[93]

Our proposed study, based on our preliminary work, uses a careful iterative process guided by the Health-ITUEM to refine and test a mHealth intervention for improving outcomes for youth across the HIV care

continuum. The project will develop and test the mLab App, an innovative mobile and connected technology that combines HIV prevention information, with push notification reminders for testing, mobile phone imaging of a lateral flow diagnostic assay (OraQuick) and automated image processing to provide accessible, objective, secure, and real-time feedback on test results. The mLab App also contains an automated data collection and results reporting feature. The reporting feature relays test results back to the research team, triggering messages to encourage future repeat testing for a non-reactive test or for a reactive test, linkage to confirmatory testing and treatment. The proposed study is highly significant as summarized below:

- Mobile and connected point-of-care diagnostics are promising tools to increase the uptake of HIV self-testing with the goal to improve diagnosis of previouslyundiagnosed individuals and link youth to care.
- This project focuses on increasing HIV testing in one the highest risk populations–Black and Latino YMSM and YTGW (18-29 years).
- The study is designed to answer the most important question that will drive this technology forward: Will the mLab App improve the uptake of the HIV self-test in previously undiagnosed youth?

Preliminary Data: We have conducted four preliminary studies to support the use of this intervention for youth.

1) Dr. Schnall led a CDC cooperative agreement (U01 PS004975) using critical iterative end-user feedback to design a mobile app for promoting HIV prevention behaviors in high-risk MSM.[35] The methodological details, associated findings, and final Design Document have been widely disseminated.[94] Findings from this study guided the content of the mLab App, which is being refined in this proposed study.

2) Dr. Schnall conducted a study using in-depth interviews, observations, and a think-aloud protocol to understand high-risk young adults' use of the rapid (HIV) self-test. Our study incorporated a performance record to carefully identify competency in self-administration of the test.[84] This study provided evidence of the perceived usefulness of the self-test by young adults, especially in light of their concerns about lack of privacy in medical settings. Notably, only one (of 21) participants followed all of the instructions for using the test. The policy implications of this finding are important since the FDA requirements for labelling and packaging are critical for the safe use of devices, but at the same time, end-users' abilities to understand and use these package inserts, especially in stressful situations, must be better considered.[84] To address this need, we have developed the mLab App which provides step bystep instructions on the smartphone screen and also an imaging algorithm for interpretation of test results so that the participants can be less burdened by the interpretation of fuzzy red lines, a common and well-known limitation to the self-test.

3) Dr. Scherr's team published its work on smartphone integration of a number of existing technologies as an attractive tool for standardized detection and reporting of infectious diseases. Dr. Scherr demonstrated that using an unmodified mobile phone to photograph rapid detection lateral flow assays is superior to visual interpretation by inexperienced users. In short, the photo imaging algorithm has been successfully used with lateral flow assay tests for malaria in with untrained users in non-clinical settings.[37] Dr. Scherr's work demonstrated that an automated image processing algorithm has an improved limit of detection over a commercially available lateral flow reader and reduced reporting errors inherent in visual test interpretation.

4) To understand high-risk YMSM and YTGW's plans for using the mLab App, barriers to use, and feasibility of using the imaging algorithm (the mLab), Drs. Schnall and Scherr conducted a mixed methods observational study among 18 YMSM and YTGW (mean age 24) who have all engaged in high-risk sexual behavior (unprotected anal sex) in the past 3 months. Participants used the mLab App and then completed a follow-up survey and an in-depth interview. Participants completed the Health-ITUES survey and rated the mLab App as *Impact on health* (4.3 out of 5), *Useful* (4.4 out of 5) and *Easy to Use* (4.4 out of 5). We collected paradata as part of our pilot study and collected time stamps, pages accessed, test image, type of Internet browser, operating system, and the smartphone device. This paradata mirrors the data that will be captured in Aim 3 and analyzed alongside our primary outcome data. Following the survey, we conducted in-depth interviews to understand high-risk youth's plans for using the mLab App and barriers to use. All of the participants reported this would be a very useful tool for high-risk youth and thought most youth would want to use the mLab App. They also all indicated they would seek follow-up care if they themselves tested positive and saw the principal advantages of the mLab App as being "convenient and portable" and an enabler for promoting uptake of HIV testing. In particular, youth noted that the mLab would be especially helpful to youth who did not have a close relationship

with a provider or were concerned of potential stigma from a provider regarding their sexual behavior. One participant described "the anxiety he feels during the week that he's waiting for his results and that the mLab App would offer him 'peace of mind' as the results are delivered faster." He specifically mentioned the mLab App could have a significant impact among the Latino MSM, as getting tested at the doctor's office is associated with issues such as "stigma, fear, discrimination, and homophobia." Another respondent described the *usefulness* of the app and stated "mLab App would be great for young MSM because of their smartphone use." He also thought the app would be of great use for individuals without a clinic where they can regularly get tested or for those who simply do not like to get tested. A participant who is a public health student and very knowledgeable about HIV testing and prevention explained that he "liked the mLab App and that there was no other tech like it". Another participant reported that he liked "that you can enter your zip code in the 'STI' resources page to find the nearest clinic to get tested and that this is especially important if users would like to get a follow-up test." Participants also provided useful feedback on the user interface with suggestions such as that words (i.e., "positive") appear inside the box with the visualization of the result (i.e. "+") and avoiding red/green to reduce stigmatizing implications. In summary, given our preliminary data supporting the feasibility and acceptability of the mLab App, we believe the proposed research formally testing the efficacy of the mLab App is the next logical step in research designed to improve HIV testing and linkage to care outcomes in YMSM and YTGW.

Study Procedures

Overall approach. We will first use the design specifications from our preliminary work to refine the user interface of a functional app which incorporates automated image processing of HIV test results (mLab App) and assess its usability. We will then enroll 525 Black and Latino youth (inclusive of YMSM and YTGW age 18-29 years) in a 12 month RCT to assess differences in HIV testing rates and linkage to care between the intervention (mLab App)-arm 1;standard of care HIV information control-arm 2; HIV home tests-arm 3. We will analyze paradata to understand the effect of user engagement of the mLab App on improving HIV testing rates and linkage to care.

Scientific Premise. YMSM and YTGW currently face barriers to HIV testing in clinics (e.g., socioeconomic

Overview of Study Aims, Design and Methods. Table 1 presents an overview of the design, participants, and data analysis plan for each aim.

Table 1. Overview of Design, Methods, Participants, and Data Analysis

Aim	Design/Methods	Participants	Data Analysis
1	Usability Evaluation	Heuristic evaluation: human-computer interaction experts (N=5); End-User testing: YMSM and YTGW (N=20); Youth Advisory Board (N=10)	Quantitative and qualitative summary of heuristic violations; thematic analysis of think-aloud protocol, quantitative summary of mouse clicks, time, etc.
2	Randomized controlled design	High-risk YMSM and YTGW (N=525; arm 1 n=210, arm 2 n=210, arm 3 n=105)	Descriptive statistics; Linear regression model
3	Analysis of Para Data	Data Collected through Participant use of the mLab App (N=210)	

Scientific Rigor. We will use a careful iterative process to refine the usability and test the efficacy of the mLab App for increasing the uptake of rapid home HIV self-testing. To increase scientific rigor we will: 1) have an image of the participants' OraQuick test result ensuring the validity of self-reported testing collected via surveys; 2) use validated measures; 3) use a randomized design to reduce bias in study arm assignment; 4) exercise extensive retention efforts to achieve high retention and reduce selection bias; 5) publish our design and analysis plan on clinicaltrials.gov before we commence data collection; 6) publish anonymized public use data sets after primary analyses are reported. Consideration of sex as a biological variable. We do not aim to

evaluate sex differences; the justification for only including assignment of male sex at birth is that the epidemiologic data demonstrate a clear, disproportionate impact of HIV on young racial and ethnic minority men.

Aim 1: Refine the mLab App – a mobile and connected health intervention for increasing the uptake of rapid home HIV self-testing and linkage to care – by employing rapid cycle iterative design methods with feedback from human computer interaction experts (N=5), end-users (N=20), and youth advisory board members (N=10). There are three steps with refinements to the mLab App following each step. Step 1. Heuristic Evaluation with experts, Step 2. End-User Usability Evaluation. Step 3. Review by YAB. Note the Youth Advisory Board members will not be self-testing. They will only review the content and function of the app.

Usability Testing. The goal of the usability evaluation is to refine the mLab App User interface. Usability Testing will promote improving the quality of the user's interaction with and perceptions of the mLab App.
Step 1. Heuristic Evaluation. We will conduct a Heuristic Evaluation with five informaticians who will participate as usability experts and must have training in human-computer interaction and have published in the field of informatics.
Procedures.
Heuristic Evaluators will be asked to complete a short demographic survey. Following completion of the survey, the usability experts will be asked to use the Oraquick test and also the mLab App.

The mLab App is mobile app that is accessible using a login name and password. The app will provide HIV prevention information, push notification reminders for testing, step-by-step instructions for using the OraQuick HIV tests, an image upload function to send an image of your OraQuick HIV test to the study team.

Participants will:

a) be asked to manually enter the Oraquick test results; and
b) take a picture of the test results for the app to analyze the results; and
c) receive the app's interpretation of the Oraquick test results.

By using the app, we are asking participants to help test the app's ability to interpret the results of the OraQuick tests. If you test HIV positive by the OraQuick HIV test and/or the mLab app will provide information on how to set up follow-up confirmatory testing within the following 24 hours. All information within the app will be stored on a secured server at Vanderbilt University.

While Morae Software is recording their actions, participants will be asked to use the following use cases while using the app.

First Login

1) Taking A Test
    a. If it's your first time loggingin, it's time for a test, click on the "New Test" tab
        i. Watch the video
        ii. Read the instructions and make sure you are clear on how to complete your OraQuick test (If you need additional help please click the "Help" tab)
        iii. Do the Oraquick test
        iv. Click on the start timer
        v. Do a task you find relaxing for the duration of the timer
        vi. Read your results and enter what you think they are
        vii. Get your results on the results page
2) Other tasks:

a. Check for nearby services
b. Contact us to ask a question
c. Check history
d. Look at the HIV facts on the homepage and save the ones you like
e. Read and watch videos on PEP and PrEP
f. Check your inbox for messages
g. Look at your timeline on the homepage for the date of your next test

3) Logout

Second Login

1) Check the Testing Timeline on the Homepage to see when your next test should be
2) Check history under the Test History tab after getting back the results
3) Check for nearby services
4) Contact us to ask a question
5) Check history under the Test History tab
6) If it's not time for a test, you can:
   a. Look at your timeline on the homepage for the date of your next test
   b. Check your inbox for messages
7) Logout

Heuristic evaluators will be asked to evaluate the mLab App interface using the Heuristic Evaluation Checklist and to think-aloud while they perform the usability testing.[95] The process will be recorded using Morae software,[96] which allows the researcher to record and analyze the audio recording and screen shots that are captured during the heuristic evaluation. Instrument. Nielsen[97] proposed a list of ten recommended heuristics for a usable interface design. Bright et al.[98] developed a Heuristic Evaluation Checklist based on Nielsen's ten heuristics. For the purpose of this study, the checklist will be further modified to apply to mobile devices and will be adapted based on Nielsen's heuristics for a mobile device.[95] Each heuristic will be evaluated and the overall severity of the identified heuristic violations will be rated. Data analysis. The frequencies of usability issues will be calculated according to the heuristic principles adapted from Nielsen.[99] Mean severity scores will be calculated for each heuristic principle. Evaluators' comments about usability problems on the evaluation form and the Morae recording will be grouped and content analyzed according to the usability factors of Nielsen's heuristics.[99] Dr. Schnall will review the final list of recommended changes with Drs. Garofalo and Kuhns. Finally, Dr. Scherr will review and implement the final list of recommended changes. Schnall has used this methodology in numerous mobile intervention studies and has published widely on the findings.[35, 89, 100-106]

Step 2. End-User Usability Evaluation. Study Population. Our study participants will be young men and transgender women (inclusive of YMSM and YTGW age 18-29 years) who have engaged in recent high-risk sexual behavior with a man. Inclusion criteria. (1) 18-29 years of age (see justification below); (2) assigned male sex at birth of any current gender identification; (3) understand and read English; (4) sexually active and at risk for HIV infection per CDC guidance (e.g., YMSM or YTGW and recent anal sex with men)[107](5) smartphone ownership; and (6) self-report being HIV-negative or unknown status.. Exclusion Criteria. (1) persons who have a known diagnosis of HIV; and (2) persons for whom the investigators determine that participation may be detrimental to the participant or to the study (e.g., severe cognitive deficit).
Justification for Key Inclusion/Exclusion Criteria. The proposed inclusion ages of 18-29 captures the upper range of the greatest increase in new infections,[54] and the youngest age is the average age when sexual initiation begins[108, 109] (see Inclusion of Children section). We also carefully considered inclusion of participants who are taking PrEP and will exclude participants who report taking it at baseline. While there is a growing body of literature on poor PrEP adherence, [110-112] particularly among Blacks and Latinos (NIMHD funding priority) as these are the two racial and ethnic minority groups who are most heavily burdened by HIV, [4, 6-8, 113] including those on PrEP at baseline would attenuate the intervention effect due to PrEP treatment guidelines, which

include HIV testing at 3-month intervals. We will be collecting data on PrEP use and self-reported adherence to PrEP as part of the trial. Individuals on PrEP at follow-up visits will be encouraged to follow their current treatment protocol with their PrEP provider, including HIV/STI testing requirements and medical visits. We will control for PrEP use at follow-up in all analyses.

YMSM and YTGW. We will be including BOTH YMSM who have sex with men and YTGW who have sex with men. We believe that targeting of those youth most at-risk of acquiring HIV is the most efficient strategy for implementation in practice. Based on the research to date, barriers to HIV testing for YMSM and YTGW have significant overlap,[114, 115] suggesting that the mLab App which seeks to overcome these barriers is likely to increase HIV testing uptake in both groups. Nevertheless, we will test potential differences in intervention response by race/ethnicity, sexual and gender minority status (i.e., YMSM vs. YTGW), and co-morbid conditions (i.e., depression and anxiety symptoms, history of trauma) in order to inform future tailoring or targeting of the mLab App.

Settings. This will be a multi-site study in NYC and Chicago. **NYC, NY (Schnall, MPI).**[116] In 2013, there were 117,618 persons living with HIV in NYC. Of these, 43,940 (over 37%) were infected through male to male sexual contact. Our main recruitment site will be through the Columbia University Medical Center Community Partnership for Health. In addition, we have a number of close community partners in NYC from where we will be recruiting. We work closely the LGBT Center in lower Manhattan and Ali Forney, which provides services for homeless young MSM and TGW and particularly Black and Latino youth. **Chicago, IL (Garofalo, MPI).** The 2013 rate of HIV infection diagnoses in Chicago (40.4 per 100,000) is approximately 2.5 times higher than the national rate, and the prevalence rate for Chicago (827.9/100,000) is nearly 3 times the national rate. Our main recruitment site will be through The Center for Gender, Sexuality and HIV Prevention at Lurie Children's Hospital within the Division of Adolescent Medicine, directed by Dr. Garofalo. Additionally, we will advertise the study to the entire hospital system in the Chicago area to recruit youth and collaborate with community partners who serve youth.

All of our study activities will be conducted in a private conference room at the Columbia University School of Nursing or at the Lurie Children's Hospital.

Sample. We will recruit 20 youth from both Chicago and NYC to participate in the evaluation of the mLab App interface screens. According to Faulkner,[117] 20 users are sufficient to identify 99% of usability problems. Each participant will be given $40 for participating in the usability evaluation, which is expected to take 60-90 minutes.

Participant Recruitment. We will use a multi-modal recruitment strategy. The research team has extensive experience recruiting YMSM and YTGW of color into research studies, including the pilot study of the mLab App, in which 12/18 participants (67%) were non-white and the preliminary study in which 70% were non-white (CDC U01 PS004975).

We have used a variety of recruitment venues for other similar studies and maintain strong working relationships with online advertising vendors and local community based organizations. Although online venues are constantly evolving, in the past major categories of recruitment have included social network sites (e.g., Facebook, Instagram, Twitter); online sexual networking apps (e.g., Grindr, Scruff); and banner advertisements on other websites frequented by MSM (e.g., POZ).We will recruit youth through posting flyers and promoting the study through community partners (e.g., community-based organizations – see letters of support). Those recruited through these flyers will be directed to an online web survey (e.g., REDCap) for eligibility screening.

Facebook: We will conduct targeted recruitment via Facebook. This involves targeting advertisements to all adults in the two study cities based on several factors, including interests expressed in profiles and through expressed "likes" of other posts or pages with gay and trans themes. Those who click on the Facebook ads will be referred to a brief introduction script and a self-administered online screening form with questions identical to those to be administered in venues. Grindr. We will recruit on Grindr using banner or pop-up ads that target YMSM and YTGW from NYC and Chicago. Grindr has the ability to target members who provide their race/ethnicity in their profile. Those who click on the banner ad will be directed to the brief online consent and screener to determine eligibility. BGCLive (Black Gay Chat). We will also recruit YMSM and YTGW on BGCLive using banner ads. Based on our previous recruitment, almost 90% of men recruited from their website self-identified as primarily Black. Media Sites. The study will set up an Instagram profile to promote the study, and we will also advertise through Tumbler, Yikyak, Periscope, and Snapchat. Craigslist Advertisements. We

will post free daily ads on Craigslist, in both the Volunteers and Seeking Men sections.
Those who click on the banner ad will be directed to the brief online consent and screener to determine eligibility.
Alternatives and Limitations. We decided against using respondent driven sampling (RDS) due to risk of bias because there are known social networks in our study population.[118] Although it has been reported that if certain conditions are met and if the appropriate estimation procedures are used, bias can be minimized,[119] in our previous study, "Crew 450" with YMSM (ages 16-20) (R01 DA025548; MPI: Garofalo), RDS resulted in an inefficient rate of recruitment, and the technique was ineffective in generating a representative sample.[120, 121]

Procedures for usability testing with 20 end users.
Prior to the start of usability testing, participants will be asked to complete a demographic and behavioral survey entitled mLab usability demographics.

Following their completion of the survey, participants will be given an Oraquick test and access to the mLab App. The mLab App is mobile app that is accessible using a login name and password. The app will provide HIV prevention information, push notification reminders for testing, step-by-step instructions for using the OraQuick HIV tests, an image upload function to send an image of your OraQuick HIV test to the study team.

By using the app, we are asking participants to help test the app's ability to interpret the results of the OraQuick tests. If you test HIV positive by the OraQuick HIV test and/or the mLab app will provide information on how to set up follow-up confirmatory testing within the following 24 hours. All information within the app will be stored on a secured server at Vanderbilt University.

Each participant will use the mLab App at the study site. The mLab App is mobile app on your phone that is accessible using a login name and password. The app will provide HIV prevention information, push notification reminders for testing, step-by-step instructions for using the OraQuick HIV tests, an image upload function to send an image of your OraQuick HIV test to the study team.

Participants will be asked to:

a) manually enter the Oraquick test results; and
b) take a picture of the test results for the app to analyze the results
c) you will receive the app's interpretation of the Oraquick test results.

By using the app, we are asking participants to help test the app's ability to interpret the results of the OraQuick tests. If you test HIV positive by the OraQuick HIV test and/or the mLab app will provide information on how to set up follow-up confirmatory testing within the following 24 hours. All information that you provide within the app will be stored on a secured server at Vanderbilt University

We will use Morae software™ and a think-aloud protocol that asks participants to say whatever they are looking at, thinking, doing, and feeling as they go about their task.[122-124] Before we start the task of using the mLab App, we will first explain the think-aloud protocol to the participants and ask them to do the simple practice task of counting the windows in their house/apartment while thinking aloud. The skills demonstration session will be videotaped so that the research team can assess the participant's performance, similar to the one that we created in our work with the HIV OraQuick Test.[78, 84]

During the think-aloud procedures participants will be asked to complete the following use cases:
mLab Use Cases

First Login

4) Taking A Test
    a. If it's your first time loggingin, it's time for a test, click on the "New Test" tab
        i. Watch the video
        ii. Read the instructions and make sure you are clear on how to complete your OraQuicktest (If you need additional help please click the "Help" tab)
        iii. Do the Oraquick test
        iv. Click on the start timer
        v. Do a task you find relaxing for the duration of the timer
        vi. Read your results and enter what you think they are
        vii. Get your results on the results page
5) Other tasks:
    a. Check for nearby services
    b. Contact us to ask a question
    c. Check history
    d. Look at the HIV facts on the homepage and save the ones you like
    e. Read and watch videos on PEP and PrEP
    f. Check your inbox for messages
    g. Look at your timeline on the homepage for the date of your next test
6) Logout

Second Login

8) Check the Testing Timeline on the Homepage to see when your next test should be
9) Check history under the Test History tab after getting back theresults
10) Check for nearby services
11) Contact us to ask a question
12) Check history under the Test History tab
13) If it's not time for a test, you can:
    a. Look at your timeline on the homepage for the date of your next test
    b. Check your inbox for messages
14) Logout

If a participant is HIV positive, the study team member will refer them to the HIV clinic (Dr. Garofalo [MPI] in Chicago; Dr. Olender [Co-I] in New York) for further evaluation and treatment (See Protection of Human Subjects Section). Participants will upload images of their test results through the mLab App.
We will also ask participants to answer the following open-ended questions.

Thinking back the mLab app, how would you apply this information, lessons, or activities in your own life?

Probes:

-How well does the app address the things that concern you most right now?

-How do you believe the material from the app has context to "real life"?

-What particular information or activities were most useful to you personally?

-How well could you apply the information from the app to a situation(s) that you encounter on a day-to-day basis?

How do you perceive this app would be of relevance to other young adult MSM and TGW?

Potential Probes:

-How well does the app address the things that concern your friends most right now?

-What particular elements do you believe are most useful to the young adult MSM community more generally?

-How age-appropriate were the content and activities?

Following completion of the think-aloud protocol and interview questions, participants will complete a usability questionnaire comprised of the Health Information Technology (IT) Usability Evaluation Scale (Health-ITUES).[93, 125] and the PSSUQ.

Data Analysis. Think-aloud data from the skills assessment will be coded by graduate research assistants under the guidance of Dr. Schnall. The analysis will be based on the Morae recordings of user sessions. The mean task performance time will be calculated. The researcher will search for critical incidents which will be characterized by comments (i.e., Please help; difficulties using the system), silence, and repetitive actions. Through the observation of the use of the mLab App and review of the videos by the PI and graduate research assistants, we will be able to capture rich data about participants' problems using the mLab. The analysis will be based on the Morae recordings of user sessions, transcriptions, field notes, and the user surveys. Content analysis, a technique for making replicative and valid inferences from data, will be performed.

Step 3. Review with YAB. Drs. Schnall and Garofalo will facilitate the review of the mLab App user interface, content, and function with the YAB. Through our review, we will ensure that the mLab App is culturally appropriate for both YMSM and YTGW. Dr. Schnall will insert changes directly into the mLab App mock-ups viewed on a screen, supplemented by note-taking by study staff and audio-recorded. This allows us to confirm meaning, make revisions as necessary, and reach consensus with the YAB. Dr. Garofalo will probe for further discussion on feasible ways forward and to ensure that the mLab App meets the current prevention guidelines. We will incorporate the recommended changes. As a final step, we will have members of the YAB test the final mLab App after the meeting in their own settings (e.g., Home) and return any comments or additional edits within 2 weeks. Final recommendations for the user interface will be shared with Dr. Scherr, who will work with his team and the graphic design team at Little Green Software (see letter of support) to make the final updates to the app.

Aim 2: Evaluate the efficacy of the mLab App in improving both HIV testing rates and linkage to care versus standard preventive care in 525 Black, Latino and other young men and transgender women (inclusive of YMSM and YTGW age 18-29 years) in a 12-month multi-site trial, with randomization at each site to three groups arm 1: intervention (mLab App) (N=210); arm 2: standard of care HIV information control arm (N=210); arm 3: OraQuick home test kits only (N=105).

Hypothesis 1. Youth randomized to the **mLab App** *arm, as compared to youth in the standard of care HIV information control arm, will have: a) increased rates of HIV testing within the first 6 months of the trial; and b) increased rates of re-testing in months 7-12 of the trial.*

Hypothesis 2. The total number of youth who test HIV positive and link to care in the mLab App arm will be greater as compared to the standard of care HIV information control arm.

Hypothesis 3. The image processing in the mLab App will: 1) have no statistically significant difference in sensitivity or specificity when compared to confirmatory testing, 2) have greater sensitivity and specificity when compared to the user-submitted self-analyses.

Design Overview. A randomized controlled trial will be conducted with 525 young men over 12 months. Participants will be randomly assigned to the mLab App arm 1 (intervention) or a control arm 2 (standard of care HIV testing information arm) or arm 3 (OraQuick HIV home tests).[127] Participants in arm 1 will receive access to the mLab app and HIV home test kits, those in arm 2 will receive standard of care HIV information only. The primary comparison will be between arms 1 and 2. Participants in arm 3 will receive HIV home tests kits, but not access to the mLab app. Participants in all arms will receive standard preventive care at baseline.

Recruitment. Our recruitment activities will mirror those described in Aim 1. Step 2. We will recruit youth from both Chicago and NYC as well as the entire state of Illinois and neighboring states of Wisconsin,

Michigan and Indiana in the Midwest; and all of the state of New York and neighboring states of Connecticut and New Jersey. We will recruit on Grindr and other social media using banner or pop-up ads that target YMSM and YTGW from these areas.

Sample. Our sample will include 525 Black, Latino, and other young men and transgender women (inclusive of YMSM and YTGW aged 18-29 years), with Chicago: N=180 and New York: N =345; representing the population size of each city.[128] **Statistical power and sample size calculation.** This study will use a 2:2:1 RCT design. We plan to recruit total 525 subjects (210, 210, and 105 will be in arm 1, 2, and 3, respectively). The power and sample size calculations are based on the comparison of HIV testing rates in the mLab App arm compared to the standard of care HIV information control arm for Hypothesis 1 (i.e., compare HIV testing at 6 months and re-testing during 7 to 12 months). We calculated the statistical power to detect a difference across all participants (YMSM and YTGW). Our study is not powered to detect differences in outcomes in YMSM and YTGW separately but we will analyze differences in effect by gender identity (see Data Analysis Section below). The effect size is calculated based on the findings from the FORTH RCT[75] in which self-testing resulted in a two times increase in frequency of HIV testing in high-risk MSM, and a nearly four times increase in non-recent testers compared with standard care, without reducing the frequency of facility-based HIV testing. Using a Poisson distribution, we estimated a 40% HIV testing rate over 6 months for the control group and approximately 60% HIV testing rate for the intervention group. We are using a more conservative effect size than the one **reported** previously by assuming 60% testing rate for the intervention as compared to 85% in the FORTH RCT study.[75] This 20% difference is equivalent to a medium effect size. All power calculations are based on alpha=0.05 and two-sided tests of the primary comparison and an attrition rate of 20% at 6 and 12 months. We will have at least 80% power for Hypothesis 1, to conduct two tests simultaneously (i.e., to compare HIV testing rate during the first 6 months and to compare re-testing rate during 7 to 12 months).

Eligibility criteria. In addition to the eligibility criteria listed in Aim 1 – End-User Usability Testing, we will also include the following eligibility criteria: 1) understand the limitations of the OraQuick test and the mLab App (e.g., a confirmatory test is needed – see Protection of Human Subjects); 2) not having been tested for HIV in the past 6 months (e.g., therefore being somewhat outside of the current CDC testing recommendations for high-risk populations – see below). 3) not currently taking PrEP and 4) receive a non-reactive result on the rapid HIV test at the baseline visit

Alternatives and Potential Limitations. *We carefully considered the frequency of testing for our study participants and have agreed that participants should test at least every 3-6 months based on the following 2 considerations:* 1) Current CDC guidelines recommend annual testing and more frequent (every 3-6 months) for sexually active MSM at high-risk for HIV infection based on individual risk factors.[129, 130] 2) Since all of our participants meet the criteria for use of PrEP[107] and based on our clinical experience for interpretation of these guidelines, we have specified that our study participants should test a minimum of every 3-6 months.[27,28] As part of the intervention, participants in arm 1 will be reminded to use the OraQuick tests at 3 month, 6 month, 9 month, and 12 month time points through the mLab app.

Study Enrollment. Study participants will come in to our study site in NYC or Chicago to provide informed consent, enroll, and complete a self-administered baseline survey on an iPad. Prior to enrollment into the RCT participants will be consented to screen and administered a rapid HIV test to determine eligibility. If a participant is found to be preliminary positive in the screening procedures they will be linked to care at NYP in New York or Lurie Children's Hospital in Chicago or a healthcare provider of their choice. If they are non-reactive they will be randomized and enrolled into the trial. The *baseline survey* will include questions on demographic characteristics; health literacy[131]; sexual risk behaviors including number of men (and women) they engaged in anal or oral sex with, condomless anal intercourse, as well as their HIV testing history and opinions regarding HIV testing. The baseline survey will also include questions on PEP/PrEP use and adherence, drug and alcohol use,[132] and the HIV Risk Index.[133] After completing the baseline survey, study participants in all three study arms will receive condoms, an information sheet on HIV prevention, PrEP assessment, referral information for clinics that provide PrEP, and a card with the study team's contact information and the NYP/Columbia Comprehensive Care Clinic Phone/Text Number (NYC) and Northwestern/Lurie Children's Hospital (Chicago).

Randomization. After providing informed consent, youth will be randomized to study arms in a 2:2:1 ratio of : arm 1-mLab App (2), arm 2-Standard of Care HIV information arm (2), arm 3-HIV home tests (1). We will use

stratified randomization[134] to ensure equal representation between treatment groups at each study site (Chicago vs. NYC).[135] To reduce opportunities for selection bias, we will use a variable permuted randomization block design[136] where the block size itself is randomly selected (i.e., blocks of five to ten). The advantage of the permuted block design is that treatment assignment is pre-determined before the trial begins and then assignment remains static throughout the course of the trial.[137] Within each city stratum, a computer program will randomly assign each participant to the next treatment allocation from a random-permuted block randomized sequence. All **three arms** will receive standard-of-care HIV/STI testing-related risk reduction counseling, a box of condoms, PrEP assessment, and referral information for clinics that provide PrEP.

Alternatives and Potential Limitations. Given that participants must be HIV negative to participate in the study, HIV testing will be included as the final screening component to verify study status prior to enrolling. This will help ensure that participants are not falsifying information on their screeners to enroll in the study. Importantly, participants are expected to continue normal healthcare activities during the course of the study and to be offered HIV testing referral information and on-site testing through existing service providers.

Arm 2- Standard of care HIV information control arm. Youth will receive standard-of-care HIV/STI testing-related risk reduction counseling, a box of condoms, PrEP assessment, and referral information for clinics that provide PrEP during your first visit. Youth randomized to arm 2, standard of care control, will be sent an email or text with links to mobile-optimized online prevention information, including PrEP and HIV testing information that is found on the CDC website. [127] They will also receive a study information card listing the Columbia University School of Nursing / Lurie Children's study teams' contact information. Once youth are randomized, they will be analyzed according to their original assignment (i.e., intent-to-treat).

Arm 3-HIV home testing arm. Youth randomized to arm 3 will be provided with the 2 OraQuick tests (including the package insert), and a box of condoms to take home at baseline. They will receive 2 more OraQuick tests at the 6 month visit. Participants may come in person to receive their tests or their tests may be mailed to them at their verified address if they are unable to complete an in-person 6 month visit. OraQuick tests will be sent via tracked shipping through USPS, FedEX, UPS. At their baseline appointment, youth will also be sent an email or text with links to mobile-optimized online prevention information, including PrEP and HIV testing information that is found on the CDC website. They will also receive a study information card listing the Columbia University School of Nursing / Lurie Children's study teams' contact information

Arm 1-Intervention Arm (mLab App + HIV home test). Youth randomized to the intervention arm will be provided with the mLab App, 2 OraQuick tests (including the package insert), and a box of condoms to take home at baseline. They will receive 2 more OraQuick tests at their 6 month visit. Participants may come in person to receive their tests or their tests may be mailed to them at their verified address if they are unable to complete the in-person visit. The OraQuick tests will be sent via tracked shipping through USPS, FedEx, and UPS. At their baseline appointment, youth will also be sent an email or text with links to mobile-optimized online prevention information, including PrEP and HIV testing information that is found on the CDC website. They will also receive a study information card listing the Columbia University School of Nursing / Lurie Children's study teams' contact information. The goal of the mLab App is not for partner testing. We will advise participants upon study enrollment and consent (see Protection of Human Subjects) that the technology is NOT to be used for this purpose in this study. Given this limitation, we will suggest that participants who have partners who are interested in testing should contact the study team in each respective city for more information on HIV testing. We will also reinforce with participants that the mLab App is considered a screening device and they should seek confirmatory testing (for both negative and positive test results). The mLab App is mobile app on your phone that is accessible using a login name and password. The app will provide HIV prevention information, push notification reminders for testing, step-by-step instructions for using the OraQuick HIV tests, an image upload function to send an image of your OraQuick HIV test to the study team.

Participants will:

a) be asked to manually enter the Oraquick test results; and

b) take a picture of the test results for the app to analyze the results; and

c) receive the app's interpretation of the Oraquick test results.

By using the app, we are asking participants to help test the app's ability to interpret the results of the OraQuick tests. If you test HIV positive by the OraQuick HIV test and/or the mLab app will provide information on how to set up follow-up confirmatory testing within the following 24 hours. All information that you provide within the app will be stored on a secured server at Vanderbilt University

Reminder notifications. Participants in the intervention arm will be instructed to use the mLab App and the HIV self-test kit at 3 months, 6 months, 9 months, and 12 months after enrollment. Participants will receive a reminder push notification 2 weeks prior to their scheduled test date and 1 week after their scheduled test date.[138] In the mLab app, if a participant indicates they have received a preliminary positive HIV test using the home HIV test, participants will be directed to another screen on their smartphone directing them to call the study team or the warm line at the NYP or Lurie clinic (depending on geographic location) to receive follow-up confirmatory testing [and if needed, linkage to care]. Participants will be told that this result does not necessarily indicate that they are HIV positive (see false positive in Protection of Human Subjects), that further follow-up testing is needed, and they should contact the clinic or the study team within 24 hours. The mLab team will return the call within normal business hours. The number and nature of calls from participants to the study team (e.g., related to mLab App use, test interpretation, distress at reactive results) will all be recorded and will be reviewed yearly or at a date determined by the DSMB with our DSMB (see letters of support). We will track linkage to follow-up testing and care. Our DSMB will carefully monitor our study activities and data – see Data Safety and Monitoring Plan.**Sound Retention Efforts.** Participants will be asked after study screening what would be the best way for us to remind them of the appointment (voice phone, text, e-mail). Participant retention during the intervention will beenhanced in several ways. First, participants will be compensated for their time to complete the baseline assessment and completing the follow-up assessments. In addition, during the follow-up survey (6 months), participants will be asked to update their locator information. Using these extensive procedures promotes participant attendance at the follow-up visits, which has been shown to be successful in previous trials.[139, 140] **We have 4 levels of outcomes:** primary, secondary, intermediate, and program evaluation. The survey items are included in the Qualtrics attachment. The primary outcome for Aim 2 / study trial (Uptake of rapid HIV

self-testing) is the proportion of participants who self-report being tested for HIV in the past 6 months. The secondary goal is to collect and analyze data on the app's test interpretation performance. For the intervention arm (arm 1), we will also have data to confirm their self-report since we will have a photo image of their OraQuick test. We will assess and describe any bias in self-report of HIV testing in the intervention condition.

Follow-Up Surveys. All participants will receive a follow-up survey at 6 and 12 months after the baseline visit. The follow-up survey will be administered either in person on an iPad or, if they are unable to complete an in-person visit, remotely through a Qualtrics survey distributed via email. In total there will be three survey time points for all study participants (baseline, 6 and 12 months). Study participants will receive $40 at baseline, $55 at 6-month follow up, and $75 at 12-month follow up for the time to complete the surveys.

Data Analysis. Groups 1, 2, and 3 will be described with respect to baseline characteristics (e.g., means, standard deviations, ranges, and proportions). Before beginning formal analyses, we will examine the patterns of missing data, paying special attention to the balance of missing data in the study arms. From our prior trials, we anticipate all participants will provide baseline data, 90% will provide immediate post-intervention data, and approximately 80% will complete the 6 and 12 month post-enrollment assessment. Analysis of Intervention Effects. All multivariate analyses will be preceded by standard descriptive bivariate analyses to describe the key variables and relationships among them. These analyses will include means, frequency tables, histograms, and examination of distributions. Frequencies and rates of HIV tests, as well as corresponding confidence intervals, will be calculated for each arm. All statistical tests will be two-sided tests with the level of significance at 0.05. Hypotheses testing will be based on logistics models to compare (1) HIV testing during the first 6 months; and (2) HIV re-testing at 7-12 months between the mLab App arm and the control (*Hypothesis 1*). We will conduct stratified analyses to examine the differences in testing uptake in subgroups (i.e., racial/ethnic, age, YMSM vs. YTGW, and risk level). Effect sizes will also be compared between arms 1 and 3 to describe differences in testing and linkage behavior attributable to the mLab app with home test distribution versus home test distribution only. Linkage to care will be measured by the percent of study participants who tested positive and

attended a first HIV care appointment at NYP/Columbia or Lurie or who provide documentation of care at another clinic and the time to link to care after positive result. Follow-up surveys for HIV positive participants will also include questions regarding positive diagnosis, such as disclosure and seeking care. For participants who test HIV positive, we will compare the rates of linkage to care between the mLab App arm and the control arm using Fisher's exact test (*Hypothesis 2*). However, because the number of positive (HIV) tests is expected to be approximately 25-40, this part of the study will not have power to detect a significant statistical difference between groups.

mLab Image-Processing Evaluation Methods. During use of the mLab App, participants will submit images of their Oraquick self-test to the app for analysis by an automated image-processing algorithm. Prior to submitting this image for analysis, participants will be asked to interpret the results of the test using the instructions that are provided standard with the OraQuick test. This self-reported result will be recorded and uploaded with the user-submitted image of their rapid test. Study team members with expertise in rapid test use and analysis will evaluate the uploaded images of each rapid test, and provide an additional assessment. The user-submitted result and the study team assessment will not be used by mLab in its automated image-processing. All users that submit tests that are identified as positive, either by the automated image-processing in mLab, the study team personnel's inspection of the image of the rapid test, or by the study participant themselves, will be referred for confirmatory testing.

(Hypothesis 3).**mLab Image-Processing Data Analysis Plan.** Including the confirmatory test, which will be treated as the gold standard to determine whether a test result is truly false or positive, there will be results from four analysis methods collected on the same set of tests (1. User-submitted results, 2. Study team interpretation of uploaded images, 3. Automated mLab App results, 4. Confirmatory testing). The sensitivity and specificity for each of these methods will be compared using McNemar's test. This will result in the following statistical comparisons for both sensitivity and specificity: 1) user-submitted analysis to study team analysis, 2) user-submitted analysis to mLab analysis, 3) study team analysis of uploaded images, 4) user-submitted analysis to confirmatory testing, 5) study team analysis to confirmatory testing, 6) mLab analysis to confirmatory testing.

Missing Data. Multiple imputation (MI) methods will be applied to address missing values under the missing at random (MAR) assumption (i.e., missingness can be fully accounted for by variables with complete information).[141] These analyses will be complemented with assessment of how sensitive the inferences are to the MAR assumptions. Sensitivity analysis will be performed based on selection models for dropout.[142-144]

Intention-to-Treat (ITT) Analysis: All analyses will use the ITT principle,[145] which requires subjects' data to be analyzed as randomized, regardless of whether they used the mLab App or not.

Aim 3: Monitor and analyze paradata to understand the effect of user engagement of the mLab App on improving HIV testing rates and linkage to care.

To understand barriers and/or facilitators of its use, the mLab app will automatically collect paradata for each user interaction throughout the study. This paradata is considered "free" in that it does not require any additional effort from the user.[146] This data will be analyzed for each user, as well as aggregated to understand what component of the intervention lead to behavior change. We will specifically examine who uses the mLab App and how frequently it is used over time.

Table. Paradata Collected for Each mLab Event
1. Unique Code
2. Page accessed
3. Time stamp
4. Rapid test image
5. Internet browser type
6. Operating system
7. Device

Methods. We will capitalize on the use of the extant mLab software which is written as a mobile-friendly web application in hypertext markup language (HTML), hypertext preprocessor (PHP), JavaScript, and Python (for computer vision), and integrates with REDCap for backend data storage. On each page of the mLab app, a PHP script logs every user interaction before the page of the application is displayed to the user. Therefore, any event that would refresh or send the user to a new page (e.g., HTML links) initiates an event-driven paradata capture. The PHP script transmits the data to REDCap through the secure REDCap API.

Data Analysis. The primary paradata that will be collected is shown in Table 4. From this data, we will derive the following use data for each session: duration on each page, page progression through the application, time from login to result, number of rapid test pictures previewed before sent for result, and total time prior to logout. We will analyze the data on multiple scales and perspectives: individual-level (i.e. user-level), application-level, page-level, session-level, and how these differ by demographic characteristics, HIV testing history, technology

use, and outcomes measures. At the app-level, we will analyze timestamp data including time of day and day of the week that HIV self-testing is performed. We will also analyze the time-to-HIV self-testing result from App login -- a primary indicator of usability. Efficiency is a major construct of the Health-ITUEM model, the guiding theoretical framework for our study (see Figure 4). Additionally, we will measure the amount in bytes of user data transmitted. Importantly, longitudinal analysis will determine if user-experience changes with repeated use.

The paradata collected from each page will be analyzed to generate a "heatmap" of user-interaction (i.e., the distribution of activity for each link/button). Use of the heatmap will inform user duration on each page of the application user interaction with the HIV prevention content, the contact pages, and the help page. We will explore usability issues with consideration for how many times users accessed help, and what page of the mLab app referred them to the help, implying the need for clarification. Similarly, contact page paradata will be analyzed to determine at what point in the use of the imaging software (the mLab) users initiated contact with the study team and/or the clinic. Specifically, referring pages to the contact page will be analyzed (i.e., do users engage with contact resources only after a diagnosis is provided?). Finally, we will use paradata to understand when users disengage with the mLab app (e.g., logout after received diagnosis, logout prior to diagnosis, session timeout).

Since the mLab App provides an image-based diagnosis of HIV rapid tests, paradata will be used to understand the process of capturing a photograph for analysis. To this end, we will count the number of images previewed prior to submission of a final image for mLab analysis. Within each image, we will perform digital image analysis to determine orientation, luminosity, and major colors within an image – all factors that would indicate successful analysis in mLab. Importantly, this analysis will be used to improve the computer vision algorithm.

We will analyze difference in the aggregated data by demographic group (age, race, and risk level) to allow us to better understand engagement with the intervention and potential facilitators and barriers to mLab App use. We will evaluate if grouping by HIV status affects these results in any way (e.g., do HIV+ users engage with features differently than HIV- users?). Finally, as a web application, there is potential for slightly varied experiences on different devices or web browsers, and we will evaluate if there are differences in mLab paradata across devices and browsers.

Risks, Benefits & Monitoring
Potential Risks

The risks of participating in this study are:

We will discuss each of these risks below and describe the protection again these risk under "Adequacy of Protection Against Risks."

General Risks:

1. A risk of taking part in this study is the possibility of a loss of confidentiality or privacy, including that associated with the app on the participants' phone. Loss of privacy means having their personal information shared with individuals outside of the study team who were not supposed to see or know about their information. The study team plans to protect the privacy of participants. Their plans for keeping your information private are described in the Privacy section of Protection Against Risk.

Risks Specific to the Use of OraQuick:

1. **Subjects must follow package instructions on the OraQuick test and always read the test results from the OraQuick test themselves given that the accuracy of the mLab application has not been proven.**, Confirmatory HIV testing is still needed.
2. Participants may mistakenly believe that a negative result of the OraQuick Test means that they are not infected with HIV. There is a chance that the test does not detect an HIV infection. To offset this risk, participants will be repeatedly told that a negative result in the OraQuick test does not mean that they are not HIV infected, since infections that occurred within the prior three months may not be detected by the test, and that condoms should still be worn to avoid the risk of HIV and other STIs.
3. Participants may experience distress if they get a positive result in the OraQuick HIV test. If at any point during their participation in this studythey request a referral for a confirmatory test, we will refer them to an HIV/STI clinic for a confirmatory test and referrals for treatment and care if needed, including psychological assistance. We will assist participants in scheduling an appointment for a firstconsultation.
4. There is a risk of receiving a false positive test result, meaning participants have tested HIV positive, but are in fact HIV negative. Such participants will be instructed on the limitations of the OraQuick Test, including that false positive results have occurred, which again stresses the need for confirmatory testing since results may change. Limitations of the OraQuick Test: A potential risk of the study is that participants might mistakenly believe that the test kit protects them against HIV and/or other STIs. During the consent process, participants will be reminded that self-tests will not protect them against HIV or other sexually transmitted diseases or infections, and that they must use protection such as condoms when engaging in sexual intercourse if they want to avoid infection. Participants will also be reminded that HIV testing does not include testing for STIs. There is a small risk that a positive result is a mistake. Fewer than 1 in 100 people who get tested may receive an incorrect result. Therefore, if a participant tests positive, a second test is needed to confirm the result. If the participant receives a HIV positive result while testing during this study, we will provide confirmatory testing. Additional HIV testing will be made available to individuals who test negative and who request it.

Risks Specific to the Use of the mLab App:

1. The mLab App is not FDA-approved for this indication. Results from the mLab app are investigational and the manual read of the OraQuick In-Home Test is the result of record.
2. There may be false positive results related to the performance of the mLab App, integration withREDCap and potential problems with the usability of the overall system.
3. There may be false negative or positive results caused by issues with the imaging algorithm (e.g. lighting, geometries, and appropriately set processing thresholds).

Adequacy of Protection against Risks

a. Recruitment and Informed Consent

Recruitment for study participation will occur following approval by the CUMC IRB. The PI will determine eligibility for inclusion, explain the purpose of the study, answer any questions, and obtain written consent from the participants.

Patients who agree to participate will sign a consent form. Recruitment strategies will be developed in collaboration with clinics and community centers. Potential risks and strategies for risk management will be carefully explained as part of informed consent procedures. All HIPAA requirements will be applied to this study. The study plan, advertisements or recruitment letters, lay description of the study, and all consent forms will be submitted to the IRB following proposal acceptance and prior to study initiation. The study PIs will be responsible for obtaining IRB approval for this study.

We will inform the study participants upon enrollment that the goal of the mLab App is for self-testing and NOT for partner testing/sero-sorting. We will advise participants upon study enrollment and consent that the technology is NOT to be used for their partners during the study. Given this limitation, we will suggest that participants who have partners who are interested in testing should contact the study team for more information on HIV testing.

We will also remind participants that the mLab App is not an approved diagnostic test and recommend seeking confirmatory testing (for both negative and positive test results). Upon receiving a positive HIV test result, study participants will then be directed to another screen on their smartphone with the phone number of the Comprehensive Care Program Warm Line. Participants will be told that this result does not necessarily indicate that they are HIV-positive but that further follow-up testing is needed. Participants will also be advised to contact the Clinic or the study team within 24 hours of receiving a positive test result. The number and nature of calls from participants to the study team (e.g., related to mLab App use, test interpretation, distress at reactive results) will all be recorded. All participants will be advised to test quarterly, and will receive the referral number to the Comprehensive Care Clinic.

***b.* Protections against Risks**

This study will be submitted to the IRB before starting the study. We will be careful to ensure that no coercion occurs during the recruitment periods by ensuring the voluntary participation of both healthcare providers and patients. All participants will be screened to assess for study eligibility. Non-participation will not affect patients' medical care in any way.

1) Confidentiality: The smartphone that is connected to the mLab App will require a password. All study data, including mLab App results will be encrypted and stored on secure HIPAA-compliant servers at the Columbia University Medical Center campus. All study data will be kept in password-protected computers or file cabinets in locked offices. All study data will be maintained in a completely secure and HIPAA-compliant environment. All servers have HIPAA-compliant security. Nonetheless, there is always the risk of a data breach, so we will make our study participants aware of this risk upon enrollment.
2) False Negative Results: The mLab App has the potential for providing a false negative result, especially during the period of acute HIV infection in which a newly infected individual may be most contagious.

We will clarify these issues before giving the mLab App to participants, test their understanding of the limitations of the HIV Home Test with a structured instrument (Appendix B), provide a study information card that contains information about test limitations, and recommend use of condoms regardless of the test outcome. Upon enrollment, we will explain to participants that the mLab App cannot determine their status with 100% accuracy. The mLab App may not detect acute HIV infection.

3) Risk of receiving a false positive HIV home test result: Participants will be informed of the limitations of the mLab App, including the occurrence of false positive results. Again, the study team will stress the need for confirmatory testing.
4) Distress a participant may experience if s/he receives a positive HIV result at home: If a research subject gets a positive result in the mLab App at any point during participation in this study, this result will require confirmation. The study team will provide the participant with a confirmatory test and referrals for treatment and care if needed, including psychological assistance.
5) Window Period for Interpretation of Results: In the mLab App, wehave added in 2 points of instruction related to the 20-40 minute window period for the Oraquick results – see Appendix L, slides 7 and 11. Second the images will be time stamped and we will not return algorithm results if the time from reporting in screen 7 and the time to take a picture in screen 11 has been less than 20 minutes or more than 40 minutes.
6) Invalid Test Results: If the participant reports an invalid result – the software will send the following message back to the study participant: You reported that your results are invalid. An Invalid test result means that there was a problem running the test, either related to the specimen or to the Test Device. An Invalid test will not be interpreted by the mLab App. Repeat the test with a new Divided Pouch and a new oral fluid. Please contact the study team if you are unable to get a valid test result upon repeat testing. If the participant reports an invalid test then we will turn off the ability for the mLab App to return the algorithm results to the participants. However, invalid images will still be stored in REDCap and reviewed by the study team.
7) Imaging Algorithm: The parameter values in the mLab App's image processing algorithm have been validated and selected to primarily optimize sensitivity and specificity. However, it is possible for the mLab App to return both false positives and false negatives. The study team will monitor the images that are sent using the mLab App, and will contact study participants in the event of either: 1) the mLab App returns an incorrect result, and 2) a discrepancy between the participant's manually reported result and the mLab App result.

c. **Additional Planned Procedures for Protecting Against/Minimizing Potential Risk/Additional Protections for Children**

Procedures in the Event of a Reactive HIV Test

In the event a participant has a reactive HIV test, study team members will counsel the participant regarding the meaning of his result. Specifically, the study team will reiterate with the participant that:

1) His result is a preliminary positive and it is likely that he is infected withHIV;
2) The preliminary positive result needs to be verified with confirmatorytesting;
3) He needs to return for the results of his confirmatory testing; and
4) Resources for counseling and referral to care are available to him.

The participant will be referred for follow-up testing and care at a clinic at Columbia University Medical Center or Lurie Children's Hospital. We have clinicians on staff at the clinic who are part of our study team.

We detail below the risks and procedures undertaken to minimize them for the intervention arm.

1. **Participants must follow package instructions on the OraQuick test**. They must always read the test results from the OraQuick test themselves, given that these results are more reliable than the mLab App results and the accuracy of the mLab app results have yet to be proven. Participants will be required to report the results from the manual real and enter it into the mobile app and will be contacted either by phone or by the app's messaging portal. In addition, confirmatory HIV testing will be required if an individual provides positive test results from the manual read of OraQuick.
2. Participants may mistakenly believe that a negative result of the Oraquick Test means that they are not infected with HIV. There is a chance that the test does not detect an HIV infection. To offset this risk, study staff will remind participants upon enrollment that a negative result in the OraQuick test does not mean that they are not HIV infected, since infections that occurred within the prior three months may not be detected by the test, and that condoms should still be worn to avoid the risk of HIV and other STIs. Study staff will ask participants to explain their understanding of the meaning of a negative Oraquick test result.
3. Participants may experience distress if they get a positive result in the OraQuick HIV test. If a participant tests positive, he/she will be referred to a clinic for confirmatory testing without a request. If a participant tests negative, then we will refer only if he/she requests additional testing. If at any point during their participation in this study they request a referral for a confirmatory test, the study team will refer them to an HIV/STI clinic for a confirmatory test and referrals for treatment and care if needed, including psychological assistance. We will assist them in scheduling an appointment for a first consultation.
4. There is a risk of receiving a false positive test result, meaning they have tested HIV positive, but are in fact HIV negative. They will be instructed on the limitations of the OraQuick Test, including that false positive results have occurred, which again stresses the need for confirmatory testing since results may change. Limitations of the OraQuick Test: A potential risk of the study is that the participant might mistakenly believe that the test kit protects them against HIV and/or other STIs. It is important that they know that self-tests will not protect them against HIV or other sexually transmitted diseases or infections, and they must use protection such as condoms when engaging in sexual intercourse if they want to avoid infection. HIV testing also does not include testing for STIs. A positive result from the OraQuick Test generally indicates that HIV antibodies have been detected in their body. There is a small risk that a positive result is a mistake. Fewer than 1 in 100 people who get tested may receive an incorrect result. Therefore, if they test positive, a second test is needed to confirm the result. If participants receive a HIV positive result while testing during this study, the study team will provide them with confirmatory testing. A negative result in the OraQuick test generally means that HIV has not been detected in their body and that they are HIV uninfected. A negative result could also mean that the participant may have gotten HIV too recently for the test to detect it. Additional HIV testing will be made available to all subjects.
5. A risk of taking part in this study is the possibility of a loss of confidentiality or privacy, including that associated with the mLab app on their phone. Loss of privacy means having their personal information shared with someone who is not on the study team and was not supposed to see or know about their information. The study team plans to protect the participants' privacy by storing all data on locked computers in locked facilities on secure servers hosted by Columbia University Medical Center. The servers are HIPAA compliance and set to conform to the current industry standards for storing Personal Health Information (PHI)

BENEFITS:

Potential Benefits of the Proposed Research to Human Subjects and Others

This study has not been designed for the direct benefit of its participants; however, there are a number of ways in which they may derive benefit. The proposed research will inform the delivery of HIV prevention messages. The knowledge gained will contribute to the body of knowledge regarding the use of health information technology for improving the lives of MSM at risk for HIV. The avoidance of HIV through study participation will be a significant personal benefit to participants.

Participants in the mLab App arm will be referred to standard-of-care services either at the time of a reactive HIV test result (if sero-positive) or the end of the study (if sero-negative). Standard-of-care services for HIV-negative MSM, regardless of risk level, includes provision of HIV/STI testing (based on the local HIV testing standard procedure) as described below. Standard-of-care services for HIV-positive MSM include provision of linkage to HIV care services based on the standard-of-care services offered in the local project site community.

Importance of the Knowledge to be Gained

Each new case of HIV constitutes a burden to the individual, the health care system of our country, and to society at large. Our study is expected to result in benefits for society since it will provide a knowledge base for HIV and STI prevention strategies. Point-of-care tests are used worldwide to screen individuals for antibodies against HIV. The risks to research participants enumerated above are reasonable in relation to the anticipated increase in knowledge on the potential use of self-testing and behavioral economics for improving outcomes across the HIV care continuum.

ALTERNATIVES:
The alternative is not to participate in the research.

DATA SAFETY MONITORING PLAN:

This study will have a data safety monitoring board (DSMB) which will meet yearly or on a schedule determined by the DSMB. The DSMB will consistof individuals who are not otherwise associated with the study who will review study progress, safety events and make recommendations to the investigative team. The DSMB will be asked to commit to 5-10 hours of time per year for meeting preparation, attendance, and report writing. They will be asked to elect a Chair who will lead the effort of the group, facilitate meetings and be responsible for report preparation. In the annual meetings,the DSMB members will review the evidence of study progress, including targeted versus actual recruitment, retention, and interim analysis of efficacy as well as review of safety events. Based on this review, the group will draft a report of recommendations to the investigators regarding current procedures and/or trial suspension in the case of safety events. The four members of the DSMB include Drs. Donenberg, Koblin, Pearson and Scrimshaw.

Geri Donenberg, PhD has extensive experience conducting NIH-funded research nationally and internationally. As Principal Investigator/Co-Principal Investigator of nine federally-funded studies, and Co-Investigator of an additional 11, Dr. Donenberg brings vast expertise in basic longitudinal research, prevention and intervention development and adaptation, evidence-based prevention program implementation, and the conduct of randomized controlled trials with primarily low-income, ethnic minority youth and families. She has published

over 80 peer-reviewed manuscripts underscoring the impact of family factors, individual attitudes and beliefs, and peer and partner characteristics related to adolescent sexual behavior and substance use, particularly youth with mental health problems and teens in the juvenile justice system. Dr. Donenberg has also published widely on youth outcomes related to HIV prevention interventions. Dr. Donenberg has been involved in numerous multi-site collaborative studies in the US and Africa, and she oversees two large research and service university-based programs designed to address HIV prevention, testing, counseling, treatment and linkage to care for underserved indigent youth and adults.

Beryl Koblin, PhD, is the Head of the Laboratory of Infectious Disease Prevention at the New York Blood Center. She has led a research group for 25 years focused on HIV epidemiology in high-risk populations and conducted numerous behavioral and biomedical intervention trials. I have designed, conducted, and analyzed numerous epidemiologic studies and intervention trials involving MSM and have been Principal Investigator over 25 grants from NIH, CDC, and private foundations. I have significant experience with conducting research with young MSM through implementing the CDC-funded Young Men's Surveys in New York City and the National HIV Behavioral Surveillance MSM survey. I led the development and implementation of HPTN 061, a feasibility study of a multicomponent intervention to reduce HIV infection largest cohort of Black MSM in the US. I am currently the Principal Investigator of an NIH-funded R01 study that seeks to develop an intervention utilizing technology to match young Black MSM to their optimal HIV testing approach

Cynthia Pearson, PhD, is a Research Associate Professor School of Social Work and Associate Director at the Indigenous Wellness Research Institute Research Core, University of Washington. Her research incorporates the complexities of HIV/AIDS risks such as sexual behavior, substance use, and trauma; and identifies strengths and protective factors that support indigenous women's wellness. Dr. Pearson reaches community members and identifies resources to create innovative sustainable interventions. Dr. Pearson has worked with communities in Mozambique, China, and indigenous communities of the Pacific Northwest. Dr. Pearson is the Principle Investigator of ETHICS: Ethics Training for Health in Indigenous Communities Study (R01HD082181). She is also a former fellow with Fordham University HIV and Drug Abuse Prevention Research Ethics Training Institute (RETI) and is a member of the Advancing Indigenous Research Ethics in Practice and Policy Committee at the University of Washington. Her expertise is in designing tribally-based health studies from an ecological perspective that emphasize social, economic, political, environmental, and historical determinants of health. Specifically, Dr. Pearson's research focuses on the intersecting risk of substance use, historical and lifetime trauma, and HIV risk and how culture, place and community serve as protective factors (R34DA034529). Dr. Pearson meets community members where they are and identifies community ways of knowing and resources to create innovative sustainable interventions. She is the principle investigator and co-investigator on multiple federally-funded grants using a community-engaged approach, closely collaborating with tribal communities across the US in the promotion of American Indians and Alaska Natives wellness.

Eric Schrimshaw PhD, is a social/health psychologist whose research focuses on the role of interpersonal relationships on health and well-being. His work and interests are focused on three aspects of social relationships. First, much of Dr. Schrimshaw's early work (including his dissertation) was focused on the beneficial role of supportive relationships and the negative impact of stigma, conflict, and rejection on mental and behavioral health outcomes. Second, Dr. Schrimshaw's work has addressed the health implications of concealing stigmatized identities. Specifically this work has focused on how self-disclosure or the communication of personal information with others has beneficial role in health and well-being, how concealment can have negative implications for health, and how non-disclosure can impede access to care and

support. Finally, most recently, Dr. Schrimshaw's work has focused on how different social environments where sexual relationships are formed may impede communication and facilitate sexual risk. Of particular interest are the use of the Internet and smartphone technologies for meeting sexual partners, the influence of these technologies on communication, and whether these technologies could contribute to sexual risk. Employing a mixed-methods approach that involves both qualitative interviewing and quantitative survey methods, his work documents the importance of interpersonal relationships for understanding mental health, substance use, and sexual risk behavior. He has addressed these issues within several populations including adults living with HIV/AIDS, gay/lesbian/bisexual adolescents, gay/bisexual men, and bisexual men "on the down low." Dr. Schrimshaw has published over 50 journal articles addressing the role of interpersonal relationships and health.

b. Procedures for Monitoring Data Management and Integrity

b.1. To protect the integrity of participants' data, the Project Coordinator will assign an ID number to all participants. The participant ID number will be used to identify data collected. Since the study has repeated follow-up visits, we will maintain a list of participants which link identifying information to study ID numbers. Only a limited number of staff members will have access to this list, which will be kept in locked files and in a password protected computer file. Other study personnel will have access on an as needed basis to perform their duties.

b.2. All research personnel will complete extensive training before they are granted access to this identifying information. Study personnel will complete training in the protection of human subjects which complies with federal guidelines delineated in 45 CFR Part 46. Personnel will also sign confidentiality statements that specify that if the participants' confidentiality is breached unintentionally that personnel will follow the procedures for reporting this breach to the Principal Investigator (PI). The confidentiality statement also states that unintentional or deliberate violations of participants' confidentiality may result in demotion or termination depending upon the severity of the event. Personnel will also participate in training with the Investigators and/or Project Coordinator regarding data safety, confidentiality of participants, limits of confidentiality, and proper administration of the study protocol.

b.3. We will store all personally identifiable data in locked cabinets. All forms containing personally identifiable information, including participant locator forms (i.e., containing contact information) will be maintained in a password-protected computer files. Data that are entered into computer files will be de-identified and maintained on a subdirectory of an institutional server with password protection. The PI will review all requests, current and future, to use the data, and any data files that are provided to other individuals will be de-identified. Data files will contain code numbers in order to make reference to particular cases across multiple assessment waves.

b.4. We will apply for a Federal Certificate of Confidentiality, and the certificate will be maintained throughout the life of the research project. We will inform study participants of the above procedures and the limits of confidentiality during the assent/consent process, prior to data collection. Specifically, we will warn participants that state law mandates reporting of abuse and/or neglect of children, and that threat of harm to self or others requires intervention by clinical staff. We will inform participants that criminal behavior (i.e., drug use) is not reported to authorities, and that the security of this information is protected by the Federal Certificate of Confidentiality.

b.5. Plan for Privacy and Security Protections. Beginning with the development process and throughout the research project, we will follow the privacy and security principles set forth at healthhit.gov. Our team is familiar with the importance of the privacy and security of personal health information to engender individual trust in the use of health information technology (HIT) applications. We have expertise and experience in this domain as we have developed a number of HIT systems for persons from high-risk populations, including those who live with HIV, whose personal health information is usually held to higher security standards than traditional patients. Most recently, we built the web-based MyPEEPS system which is housed on the Columbia University Medical Center (CUMC) IT servers. All servers are located in a secure datacenter, with necessary redundancies. Currently the network can be accessed remotely via VPN with a Citrix solution being developed. All servers have HIPAA compliant security.

c. Reporting Procedures

All adverse events will be reported per the requirements of the CUMC IRB. Should any physical or psychological manifestation be exhibited at any time during the study, Dr. Schnall will consult with her co-investigators regarding clinical situations as they arise. If there are any serious adverse events, the PI will complete an adverse event form and report to the CUMC IRB within 48-72 hours. Once the PI notifies the CUMC IRB, they will be required to report any of the following to the NIH in a timely fashion:

a. Unanticipated problems or unexpected serious adverse events that may be related to the study protocol (within 48-72 hours)

b. IRB-approved revisions to the study protocol that indicate a change in risk for participants

c. A summary of recommendations made by the DSMB or other monitoring entity and the action plan for response

d. Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions

To further ensure protection of human subjects, we have devised our Data Safety and Monitoring Plan so that it follows policies and procedures in place at Columbia University Medical Center.

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