Official Title of Study: Brief, web-based intervention to reduce heavy drinking and encourage prevention among high-risk men completing HIV/STI self-testing

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3.C.3. Randomized Controlled Effectiveness Trial

3.C.3.1. Recruitment Areas and Methods. After start-up, we will recruit 360 heavy drinking, high-risk MSM from several gay-oriented smartphone dating applications (e.g., Grindr, Jack'd, Scruff) and social networking sites (e.g., Facebook, Instagram, Twitter) in five major US cities: Atlanta, Los Angeles, Miami, New Orleans, and Washington D.C./Baltimore. We chose these areas due to their high HIV prevalence, MSM living with undiagnosed HIV, and substantial populations of African American and Hispanic/Latino MSM (see Table 3). Each of the identified advertising platforms allows researchers to focus their ads toward users in specific cities (e.g., ≤ 30 miles of city center), and we will adjust our ad strategy as needed to recruit as evenly across each area as possible. We have been using a similar approach in several ongoing studies in other cities and have pre-screened 5,135 MSM over 4 years (see §3.C.6. for feasibility details). See Table 5 (Forms E, §2.7) for recruitment timeline.

TABLE 3. Estimates of relevant participant characteristics in each geographic area

	Undiagnosed HIV per 100 MSM rate[115]	Est. male same sex couples[116]	% of population[126]	
			AA	H/L
Atlanta	1.62	107,312	28.9	6.5
Los Angeles	0.71	241,370	7.6	40.3
Miami	1.35	116,308	20.4	40.3
New Orleans	2.08	21,162	37.5	4.4
D.C./Baltimore	1.03	159,598	26.2	6.4

3.C.3.2. Participants. Eligible participants will be (1) assigned male sex at birth, (2) currently male gender, (3) 18+ years old, (4) HIV-negative or unknown status, (5) able to speak and read English or Spanish fluently, and report (6) drinking heavily within the past month, defined according to NIAAA guidelines as having drank ≥5 drinks on a single occasion at least once or an average of ≥14 drinks in a given week[127]. Participants will also report (7) not being currently prescribed or taking PrEP and (8) having met at least one of three HIV-risk-related PrEP eligibility criteria in the last 6 months[128], which include: (a) having been diagnosed with an STI, (b) currently having regular anal sex with a man who is HIV-positive, or (c) having had anal sex without a condom with a man outside of the context of a sexually exclusive relationship with a single partner who has been recently tested and is HIV-negative. We elected to recruit those not currently on PrEP given that Game Plan involves content explicitly intended to encourage users to seek a consultation about PrEP and beginning a PrEP regimen is a key risk-reduction outcome (see §3.A.4.2.). Participants will be ineligible if they report injection drug use within the past year, given that these individuals are likely to struggle with more severe dependence than can be addressed with a brief web-based intervention.

3.C.3.3. Measures. After enrolling, participants will complete a baseline questionnaire assessing demographics, HIV/STI testing history , recent sexual behavior[129-136], alcohol/drug use[130; 137], the Readiness to Change Questionnaire[138; 139], health empowerment[140], sexual motives for drinking[141], and other constructs.

3.C.3.3.1. Measures of app engagement. Several measures of app engagement will be collected as participants use Game Plan, including modules entered and completed, as well as dwell time and scroll depth on each screen[142]. Although the app stores no identifiable data, participants will use a unique study ID number on the "onboarding" screens to access content. This allows us to export all data entered via the command line on the server in order to link it with the participant database or other web applications using its Application Programming Interface (API). These data will be used to address some implementation outcomes in Aim 3, including adoption and engagement (see §3.C.4.).

3.C.3.3.2. Quarterly online questionnaires. Participants will also complete follow-up surveys online each quarter during the 12-month study period. Alcohol and drug use in the past 30 days will be assessed in these surveys using an online Timeline Followback (TLFB)[137; 143; 144]. In this task, participants are first presented with a calendar of the past 30 days, and are asked to identify days on which they drank alcohol. For each day identified, a day-level "detail view"

allows participants to report how many standard drinks they consumed (standard drink = 12 oz. beer, 5 oz. wine, and 1 oz. of liquor; a graphic "key" is provided to assist), how many hours they drank, and what their peak level of intoxication was ([1] *not at all* to [10] *extremely*) each day. Participants are then asked to identify days on which they used drugs, and for each day, which drugs they used (8 possible classes; e.g., marijuana, cocaine, prescription stimulants, etc.), and how high they were ([1] *not at all* to [10] *extremely*). Sexual behavior will be assessed using this same TLFB. Participants first identify days on which they had oral, anal, or vaginal sex. A "detail view" then guides them in reporting the number of sex partners they had on each day (up to 4), as well as each partner's gender, whether they were a new partner, were an exclusive/non-exclusive partner, whether they asked about each partner's HIV status or the last time they tested, and if so, what their status was, whether their partner was on PrEP, and whether they asked about PrEP directly prior to sex. They are then asked to report which sex acts they engaged in with each partner (oral, insertive anal, receptive anal, vaginal sex) and whether they used a condom for each act. Past studies show that online TLFBs are reliable and valid for assessing alcohol use, drug use, and sex[144-148].

Quarterly surveys will also involve detailed assessment of participants' receipt of HIV/STI testing (aside from study-provided kits), risk reduction counseling, and alcohol/drug treatment since their last survey. These surveys will also ask participants about whether they sought consultation with a healthcare provider about starting PrEP and whether they received a PrEP prescription and are taking it. For those who reported taking PrEP since the last survey, the TLFB will also assess daily adherence over the past month. Although we are aware that self-report measures of PrEP adherence have clear limitations[149; 150], these reports will primarily be used to explore possible secondary analyses of how well those on PrEP fare across the two conditions. Finally, quarterly surveys will also assess alcohol- and drug-related problems, using the AUDIT[151] and Drug Abuse Screening Test (DAST-10)[152-154], respectively. Among participants who were assigned to receive access to Game Plan and used it, 3-month surveys will also assess implementation outcomes of satisfaction (using the Client Satisfaction Questionnaire-8[155], and acceptability and appropriateness, using scales adapted from past studies[156; 157] and recommended by Proctor et al.[117].

3.C.3.3.3. HIV/STI testing. Study staff will mail CareKits to each participant at baseline, 6-months, and 12-months. CareKits are prepared by the Emory University CFAR's Prevention Science Core and, and they provide these kits and lab testing at cost to NIH-funded studies. The kits contain a urine collection cup, throat swab, rectal swab, and capillary blood collection tube, and all other supplies needed to collect valid samples (e.g., alcohol pads, lancets, etc.). An OraSure OraQuick® Rapid HIV 1/2 Antibody test is also provided to facilitate HIV testing. Each sample container is labelled with a barcode that is associated with that participant's unique study ID. Participants can also register their kits with a provided Box ID. Detailed instructions explaining how each sample should be collected, stored, and shipped are also included and presented in multiple formats (graphic, text, videos). For pharyngeal CT/GN testing, participants will be instructed to swab their tonsils and throat using a 6" sterile swab, and to seal it in a provided culture tube. For rectal CT/GN testing, they will be instructed to dab a small amount of provided lube onto a polyester swab and insert at least an 1.5 in. into their rectum and swab in a circle before sealing in a culture tube. Finally, participants will be instructed to lance their fingertip and provide about 200 mL (6-12 drops) of blood into a capillary blood collection tube. All kit contents will be shipped in provided biohazard containers via FedEx to Emory's laboratories (Atlanta, GA) to perform testing. Abbott RealTime assays will be used to test rectal, throat, and urine samples for CT/GN[158], and "classical" testing algorithms (non-treponemal, then treponemal tests) for Syphilis[159]. Once testing has been completed, results will be provided to study staff, who will then contact participants via phone within 24 hours to deliver their results. Similar to previous studies[100; 101], staff will provide a secure link and password which participants can use to access or print their certified test results and a list of local

treatment providers. Staff will monitor participants who have tested positive for any STI and follow-up with them periodically to ensure that they receive treatment. For more details on the delivery of HIV/STI results and treatment, see Human Subjects Protections, §1.b.1, 2.b.1.(4). A number of past studies show that HST is feasible, acceptable, and produces valid samples for testing[16; 17; 99-101]. In one study of MSM, 97% of genital and rectal samples collected were valid and returned to labs for analyses[100; 101].

3.C.3.3.4. Phsophatidylethanol (PEth). PEth is a phospholipid that can appear on red blood cell membranes when an enzyme that assists in membrane trafficking (phospholipase D) reacts due to alcohol exposure[160]. As such, PEth has been used as a biomarker of recent alcohol use, since the quantity of PEth produced is directly proportional to the concentration of alcohol[160]. Since PEth has a 4-day half-life[161], it may be most accurate in identifying binge drinking episodes that occur 1-4 days before sampling[31]. However, some studies have shown that PEth can accurately estimate frequent heavy drinking 2 weeks or more prior to sampling[31; 160; 162]. To facilitate PEth analysis, dried blood spot (DBS) cards will be prepared from provided capillary blood samples. DBS samples will be prepared by Emory CFAR lab staff by pipetting blood onto 903 Protein Saver Cards (Whatman/GE Healthcare, Piscataway, NJ). Cards will be dried for a minimum of 4 hours before being transferred to plastic bags with desiccant packs and a humidity indicator. Samples will then be shipped directly to US Drug Testing Laboratories (Des Plaines, IL) for PEth analysis.

3.C.3.4. Conditions. After enrollment, participants will be block randomized by geographic area and high AUDIT (≥8) scores 1:1 to two conditions. In one (1), participants will be encouraged to call a 24-hour helpline after testing that provides standard post-test counseling and referrals. In the other (2) participants will be encouraged to use the Game Plan app, but provided access to the 24-hour helpline as well. Through another project led by Dr. Wray (Contact PI; R01MH114891), we have established a 24-hour helpline of certified HIV phone test counselors that provides risk reduction counseling and referrals as part of another study involving home delivery of HIV self-tests. Risk reduction counseling provided during these calls is the same person-centered counseling approach provided in most HIV testing clinics[19], and is based on CDC guidelines[18]. It involves providing education about risk, identifying specific behaviors that put callers at risk, and devising a specific, realistic plan for reducing risk. Those in the Game Plan condition will be provided with a link to the website as well as the helpline number. In both conditions, participants will be encouraged to use these services via a large postcard included in each test kit and via email, and so, can use them after each test.

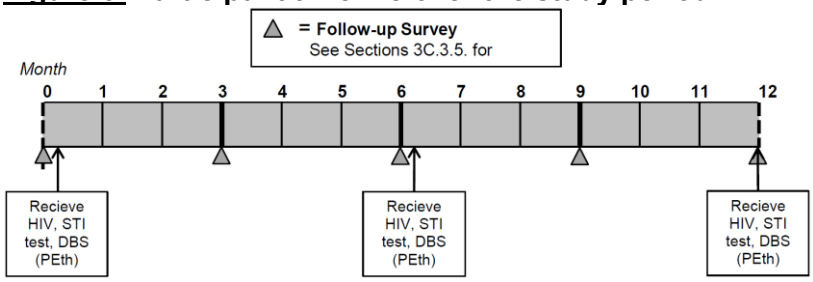
3.C.3.4.1. Game Plan – Interactive text messaging. At the end of the Game Plan intervention, users can opt-into an interactive text messaging component (developed through *TextIt*) that conducts check-ins with users about their alcohol use and HIV risk behavior each week and provides feedback about whether rates of these behaviors reflect progress toward their chosen goals. As users receive feedback over time, they can elect to change their goals, select new ones, and ask to receive information about various services via text (responses provide links to the CDC's HIV/STI testing and PrEP locator widgets). Although this program was designed to last 12 weeks, participants can elect to continue beyond this period or stop receiving messages at any time. This program is similar to that used in RC2 (REACH 2 & 3), which was in turn modeled from several previous studies of alcohol use and HIV risk behavior in MSM showing promising results[163; 164] (see §C.7.b of RC2).

3.C.3.5. Procedures. Ads recruiting MSM for a study on home-based HIV/STI testing will be placed on several MSM-oriented smartphone dating apps (e.g., Grindr, Scruff, Jack'd) and general social media sites (e.g., Facebook, Instagram). These ads will display to users who log in within 30 miles of each designated metro area. Clicking on the ad will direct users to a landing page for the study, where they can view brief details about the study and its requirements. Interested users will complete a brief questionnaire to assess eligibility. Those eligible will then be directed to provide informed consent online, as well as basic contact information, and a

baseline questionnaire (see Human Subjects Protections §2.a for details about online informed consent). Once users have consented and registered, staff will conduct a brief introductory call to verify their contact information, ensure their understanding of study requirements, and encourage adherence to follow-up procedures. After completing this call, study staff will mark these participants as 'fully enrolled,' activating them in the study database. Research staff will then prepare MyCare kits for each participant, log their PIN number and shipping information in the study database, and ship them to participants' provided home addresses with a condition-appropriate postcard (e.g., Game Plan vs. Helpline only). Email notifications will be automatically sent to participants after receiving their test kits to call or visit the website URL, as appropriate. Helpline counselors are bachelor's-level staff who are certified as HIV test counselors and are trained in crisis intervention. A Spanish-speaking counselor is on-call at all times. Counselors will record data for each helpline call in the study database. In both conditions, these procedures will be repeated for 6- and 12-month test kits.

Quarterly online follow-up surveys will use REDCap[165] and will be hosted on Brown University servers. On the date each survey is due, the study database will automatically send participants an email with language-specific instructions and links to the survey. Participants will be asked to complete these within two days, and reminder emails will be sent every other day for seven days after the due date. If participants have not completed the survey within a week of their due date, staff will contact participants by phone, text message, and email to encourage adherence. Those who fail to complete two consecutive quarterly assessments will be considered to have withdrawn from the study. Participant payments will be issued via a reloadable debit card mailed after participants are activated in the study. Participants will earn $20 for each of the five online surveys they complete over a year, plus $20 for completing each mailed HIV/STI test, with a bonus of $40 for completing all study procedures within a week of their due date, for a possible total of $200. See §3.C.6. for details about the feasibility of these procedures.

Figure 3. Participant timeline over the study period.



3.C.3.5.1. In-depth individual qualitative interviews with Game Plan users. After completing their 12-month testing and follow-up survey, 30 participants who used Game Plan will be randomly selected to participate in an individual interview via videoconferencing in exchange for an additional $25 payment. These interviews will be focused on exploring key implementation questions posed in Aim 3 in greater detail. Specifically, these interviews will be focused on eliciting major themes that affected participants' adoption, engagement, and satisfaction with Game Plan, and their sense of its appropriateness alongside HIV/STI self-testing. Facilitators will review Game Plan's components and guide participants them in discussing the fit and utility of each with self-testing. Interviews will be led by Drs. Wray and Elwy (Research Methods Core faculty), following a semi-structured format, and will last about an hour. Interviews will be audio recorded and transcribed for analysis.

3.C.3.5.2. Virtual focus groups with key stakeholders. Near the end of the effectiveness study, we will recruit 12 testing program decision-makers (i.e., from public health departments) who are considering or actively using home-based HIV/STI testing strategies in their communities from our existing contacts. In two virtual focus groups (N = 6 each), we will explore major implementation themes and anticipated barriers from the perspectives of stakeholders who would ultimately be responsible for integrating Game Plan into their testing programs. Facilitators will guide discussion on each of Proctor et al.'s[117] implementation outcomes (e.g.,

adoption, appropriateness, costs) and key concepts of the Dynamic Sustainability Framework[121] (e.g., how to achieve organizational support, long-term funding strategies, tracking program benefit) and use data collected from users during the effectiveness study to guide discussion. Facilitators will also review several of Powell's categorization of implementation strategies[166] to elicit feedback and help identify promising strategies. Finally, participants will also complete the Evidence-based Practice Attitudes Scale[167]. Focus groups will be led by Drs. Wray and Elwy, will follow a semi-structured format, will last about 90 minutes, and will be audio-recorded for later transcription. P Participants will be reimbursed $50 for their time.

3.C.4. Planned Analyses. All analyses will be led by Dr. Chrysanthopoulou (Biostatistics faculty, Research Methods Core) and will be conducted in intent-to-treat fashion[168]. Missing data for all primary and secondary outcome variables will be addressed using multiple imputation[169]. Binge drinking (BD) will consist of the number of days on which ≥ 5 standard drinks were consumed in the 30 days prior to each online follow-up. Average number of drinks per drinking day (ADPDD) will consist of the average number of standard drinks participants reported on days when they drank in the past 30 days before each follow-up. PEth, a secondary outcome, will consist of the quantity (ng/μL) detected in each DBS sample at each STI/HIV testing interval. To address Aim 1, we will (a) estimate a generalized estimating equation (GEE) with BD as an outcome and time, geographical area, condition (and their interactions), as well as problem drinking (AUDIT > 8 at baseline) and lifetime STI history as predictors. As BD is a "count" outcome, a Poisson distribution and log link function will be specified. A similar GEE model will be estimated with ADPDD, but with a normal distribution specified. Finally, we will estimate a similar GEE model with PEth as an outcome, specifically among those who reported an average of ≥ 7 drinks/day per week or at least one BD day within 2 weeks prior to sampling, excluding undetectable samples. This will allow us to explore between-group differences in PEth, specifically among those whose PEth data are likely to be most accurate. To address Aim 2, rates of new STI diagnoses will be coded as a binary variable that reflects whether any STI was detected during baseline, 6, and 12 month testing. We will then estimate a GEE model with a binomial distribution and logit link function, using STI rates at each time point as an outcome, and time, geographical area, lifetime STIs, and condition as predictors. Although we will similarly compare rates of new HIV infections across study conditions, we expect that this rate will be too low to afford meaningful comparisons. Sexual risk behavior, for the purposes of this study, will be considered any insertive or receptive anal sex with a non-exclusive partner or partner whose HIV status is uncertain without using a condom, or for those who have started PrEP, without reporting having taken a dose within 2 days of sex occurring. We chose to characterize this outcome so stringently in order to reflect sexual behavior that likely poses a risk specifically for HIV transmission. However, we will also explore condomless anal sex events with new or non-exclusive partners as a whole, since these acts are also likely to pose a risk of STI transmission. Between-group differences in PrEP uptake across the study period will be assessed using logistic regression with a binary variable representing whether participants started PrEP at any time across the year-long study as an outcome variable, and geographical area and condition as predictors. To address Aim 3, we will calculate descriptive data on Game Plan in-app use data to explore how many participants accessed it, used each module, and set behavior change goals as metrics of adoption and engagement. We will also calculate descriptive data for follow-up survey questions assessing participants' perceptions of Game Plan's appropriateness and satisfaction. Transcripts from both individual in-depth interviews and virtual focus groups will be analyzed using a directed content approach[170]. Using this approach, two independent raters (TW and RE) will review and code transcripts using NVivo, and then meet to review codes and develop a coding framework[171]. We will then use this framework to help arrive at consensus about major themes identified for each of the implementation outcomes that were addressed, first from the user (participant) perspective and then from the

stakeholder perspective. Further data collection will be conducted if needed until few new codes or themes are identified in each topic area and saturation is likely[172]. Reports prepared on these analyses will follow COREQ guidelines for qualitative research[173].