HPV Vaccine Intervention for Young Sexual Minority Men

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STUDY AIMS

This study will evaluate a mobile health (mHealth) HPV vaccine intervention (called the *Outsmart HPV* intervention) for young sexual minority men (YSMM). In doing so, we will conduct a randomized controlled trial (RCT) of unvaccinated YSMM ages 18-25 from the US recruited via social media. We will randomize YSMM to: a) standard information about HPV and HPV vaccine via a mobile-friendly website (control group); b) *Outsmart HPV* with unidirectional vaccine reminders (Out-U group); or c) *Outsmart HPV* with interactive vaccine reminders (Out-I group). Specific aims are to:

Aim 1: Determine the efficacy of the *Outsmart HPV* intervention on increasing HPV vaccine initiation and completion. Hypothesis 1a: HPV vaccine initiation (i.e., receipt of at least one dose of the three-dose HPV vaccine series) and completion (i.e., receipt of all three doses) will be higher among participants in both the Out-U and Out-I groups compared to the control group. Hypothesis 1b: HPV vaccine initiation and completion will be higher among participants in the Out-I group compared to the Out-U group.

Aim 2: Identify mediators that explain the relationship between study arm and HPV vaccine initiation and completion. Hypothesis 2: The effects of the intervention will be mediated by changes in theoretical constructs, including increased perceived vulnerability to HPV and HPV-related disease, reduced response costs of getting HPV vaccine (e.g., reduced concerns about vaccine safety and side effects), increased self-efficacy to get HPV vaccine, and increased intention to get HPV vaccine.

Aim 3: Determine if intervention efficacy differs across key demographic and health-related characteristics of participants. Hypothesis 3: Intervention effects will be stronger (i.e., moderation) among participants who are not married or in a relationship, live in urban areas, report having a routine medical check-up in the last year, or report having disclosed their sexual orientation to a healthcare provider.

FUNDING

This study is funded by the National Cancer Institute (NCI) Grant #R37CA226682 (originally awarded as Grant #R01CA226682). Please note the mHealth intervention was developed and pilot tested in a previous NCI-funded study (R21CA194831), and the current study extends this line of research.

BACKGROUND

Human papillomavirus (HPV) infections cause a significant disease burden among males. Oncogenic HPV types (mainly types 16 and 18) can cause cancers of the anus, oropharynx, and penis among males, and nononcogenic HPV types (mainly types 6 and 11) cause genital warts.[8,9] In fact, HPV causes over 90% of anal cancers and genital warts.[8,9] HPV causes about 8,000 cases of cancer and 160,000 cases of genital warts among males in the US each year.[10] Over $4 billion is spent annually in the US on treating and managing HPV-related disease.[11,12]

Table 1. HPV-Related Disparities among Sexual Minority Men

	Sexual Minority	**Heterosexual**
HPV infection prevalence (any type)[1]	**57%-93%**	26%-43%
Anal cancer incidence (cases per 100,000 population)[2-6]	**14-69**	2
History of genital warts[7]	**7%**	4%

There are over 4 million sexual minority men (i.e., reports ever having oral or anal sex with a male or being sexually attracted to males; or identifies as gay, bisexual, or queer) in the US.[13] These men have high rates of HPV infection and HPV-related disease (Table 1). At least 57% of sexual minority men have an anogenital HPV infection, which is higher than the prevalence among heterosexual men

(26%-43%).[1] Anal cancer incidence rates among sexual minority men range from 14-69 cases per 100,000 population, compared to only 2 cases per 100,000 among heterosexual men.[2-6] Genital warts are also more common among sexual minority men than heterosexual men.[7]

HPV vaccination is a promising strategy for preventing HPV-related disease, but vaccine coverage is low among males. The quadrivalent HPV vaccine (against HPV types 6, 11, 16, and 18) was licensed for US males in October 2009[14] and a 9-valent vaccine (against types 6, 11, 16, 18, 31, 33, 45, 52, and 58) was licensed in December 2014.[15] The Advisory Committee on Immunization Practices (ACIP) currently recommends routine vaccination for males ages 11-12 with catch-up vaccination for ages 13-21[16] to prevent anal cancer and genital warts.[17] Importantly, the ACIP recommends routine HPV vaccination for sexual minority men through age 26.[16] The HPV vaccine series consists of two doses if the series is initiated before turning age 15, and three doses if initiated after turning age 15.[18] Recent data suggest less than 20% of YSMM ages 18-26 in the US have received any doses of HPV vaccine.[19]

In response to the low HPV vaccine coverage among YSMM, we received funding from NCI (R21CA194831) to develop and pilot test a culturally appropriate HPV vaccine intervention for YSMM (the *Outsmart HPV* intervention). The intervention is an mHealth intervention that consists of: 1) population-targeted, individually-tailored content about HPV and HPV vaccine that is delivered via a project website; and 2) vaccination reminders sent via text message/email. For the pilot test, we used Facebook advertisements to recruit 150 YSMM from the United States. Results of the pilot study showed that *Outsmart HPV* increased both HPV vaccine initiation (45% vs. 26%) and completion (11% vs. 3%) compared to a control group. Initiation is receipt of one or more doses of the HPV vaccine series, and completion is receipt of all three doses recommended for young adults.

For the next step in this line of research, we recently received additional NCI funding (R37CA226682; originally awarded as R01CA226682) to test the intervention in a large RCT. This protocol focuses on this large RCT.

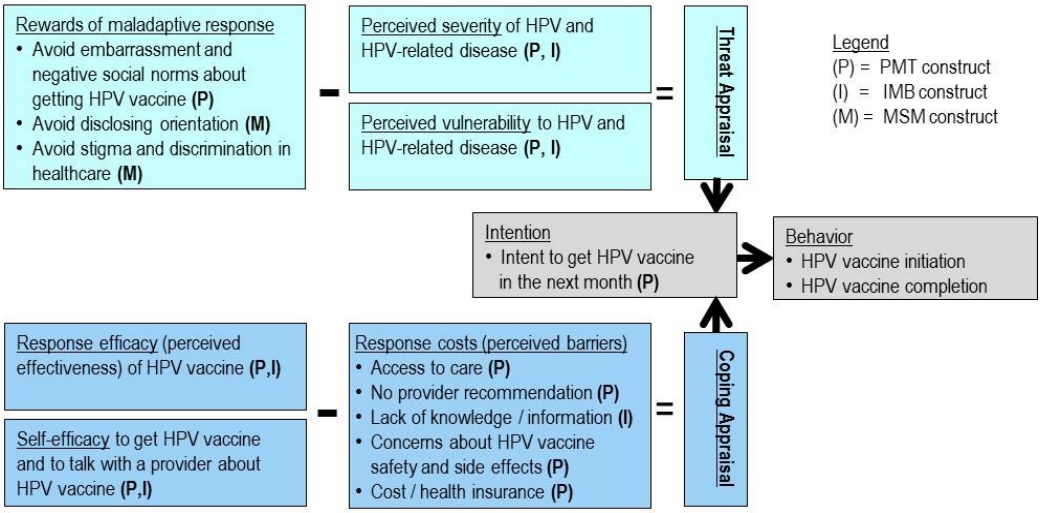
METHODS

1. Intervention Overview.

1.a. Intervention Development and Pilot Testing. We developed the *Outsmart HPV* intervention for YSMM under a previous protocol that was approved by both CSRC (OSU-15100) and IRB (2015C0079). We then pilot tested this mHealth intervention in a separate protocol (CSRC: OSU-15234 and IRB: 2016C0004). More recently, we submitted a protocol to make updates to the intervention based on results of our pilot study (CSRC: OSU-15234 and IRB: 2016C0004). The study described in this application is an extension of these prior protocols, as it will formally test the newly updated mHealth intervention in a large randomized controlled trial. The methodologies and materials included for this protocol are patterned heavily after those used successfully in our pilot study.

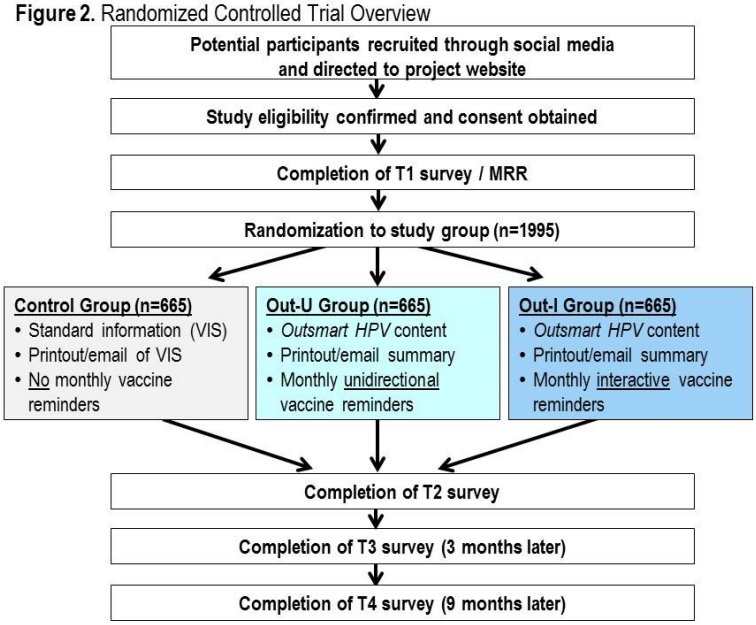
1.b. Theoretical Framework. The *Outsmart HPV* intervention was developed with a framework (Figure 1) that includes aspects of the Protection Motivation Theory (PMT),[20] Information-Motivation-Behavioral Skills Model (IMB),[21] and the Minority Stress Model (MSM).[22] The PMT is the base of the framework since it can predict vaccination behaviors,[23] but it is important to include constructs from these other models given their relevance to sexual minority health.[22,24] The PMT posits that behavior results from two parallel cognitive processes (threat and coping appraisals) and is a positive function of *perceived severity, perceived vulnerability*, *response efficacy*, and *self-efficacy*, and a negative function of the *perceived rewards of the maladaptive response* and the *response costs of the adaptive behavior*. Our framework also incorporates key IMB constructs including *information* about HPV and HPV vaccination, *motivation* for getting HPV vaccine (e.g., response efficacy), and *skills* training for increasing self-efficacy to get HPV vaccine and to talk with a provider about HPV vaccine. Lastly, the MSM posits that the health/healthcare of sexual minorities is affected by their chronic stress in a hostile social environment, and our framework includes key aspects of this model (i.e., *stigma*, *discrimination*, *concealment of sexual orientation*). We developed the *Outsmart HPV* intervention to target the constructs in this framework.

Figure 1. Theoretical Framework



2. Randomized Controlled Trial (RCT). An overview of the RCT is depicted in Figure 2.

Figure 2. Randomized Controlled Trial Overview



2.a. Eligibility/Recruitment. Eligibility criteria will include: a) cisgender male; b) ages 18-25; c) sexual minority (reports ever having oral or anal sex with a male or being sexually attracted to males; or identifies as gay, bisexual, or queer); d) lives in the US; e) has not received any doses of HPV vaccine; and f) did not participate in the pilot study. We will require men to read English and able to provide informed consent (inferred by completing the screener survey and consent form; see Section 2.b.). Age 25, instead of 26, will be the RCT's upper age limit so men do not "age out" of the recommended vaccine age range while participating in the study.

We will recruit by using advertisements (see Appendix) on social media sites, existing online panels (e.g., Amazon Mechanical Turk), and through professional contacts (e.g., co-investigators distributing approved social media advertisements). Social media sites will include some of the most frequently used sites (e.g., Facebook, Instagram).[25] We recruited via social media in our pilot study, and participants were demographically similar to nationally representative samples of YSMM.[26-28]

Potential participants will be directed to either the project website or the study's Facebook page (see Appendix). The study's Facebook page will simply serve to provide basic information about the project and then direct potential participants to the project website.

2.b. Project Website. The project website was developed for our pilot study and is a mobile-friendly website accessible by desktop/laptop, tablet, or smartphone (iOS and Android). The landing page for the project website and the information it provides about the study team can be found in an included Appendix. The portal will first ask potential participants to complete the eligibility screener (see Appendix). For those who are ineligible, they will receive a brief message thanking them for their interest in the study (see end of Appendix for eligibility screener). For those who are eligible, they will then view the consent form (which also includes the HIPAA authorization) and provide consent (see Appendix).

For eligible and consented participants, they will then be asked to create a project website username/password and provide an email address and text message number for study communications (see Appendix for Landing Page and Account Creation). After creating a username/password, participants will receive a project welcome message (see Appendix for Survey Notifications). Accounts suspected of being fraudulent (e.g., identical or similar contact information to an existing account already in the study) will be deactivated immediately and sent an account deactivation email (see Appendix).

Additional study communications will include survey notifications and vaccination reminders (Out-U and Out-I groups only), as described further in the below sections. Also as described below, the project website will also randomize participants to a study group, include online study surveys, send survey notifications, provide intervention and control group materials, send vaccination reminders (Out-U and Out-I groups only), and collect usage data.

2.c. T1 Survey. After project account setup, participants will begin their initial project website session, which will include completing the T1 (baseline) survey, viewing study materials online (either *Outsmart HPV* or control), and completing the T2 survey. The T1 survey will be completed on the project website and assess demographics, health characteristics, and theoretical constructs (about 15 minutes in duration; see Appendix). All survey items will be based on those used in past research.[19,29-35] For all survey items (for the T1-T4 surveys), a reminder will appear if a participant tries to skip an item. The reminder will say, "Please answer each question." If participants still want to skip a question after the reminder is shown, they will be allowed to. For a few items, as indicated in the appendices included with this application, participants will be required to answer the question.

2.d. Randomization. Participants will next be randomized at the individual-level to a study arm: a) standard information about HPV and HPV vaccine (control group); b) *Outsmart HPV* that includes unidirectional vaccine reminders (Out-U); or c) *Outsmart HPV* that includes interactive vaccine reminders (Out-I). A 1:1:1 allocation scheme will be used, with assignments determined by an algorithm on the project website. Recruitment will continue until 2100 YSMM are randomized (700 per study arm).

2.e. Control Group. The control group will receive standard information about HPV and HPV vaccine (see Appendix). This content will be modeled after the Vaccine Information Statement (VIS) for HPV vaccine[36] (created by the Centers for Disease Control and Prevention) and viewed by control group participants on the project website. The VIS provides basic information about HPV and HPV vaccine. We modeled the control group content after the VIS because providers are required to give patients a VIS before vaccination.[36] Thus, the VIS may be considered the "standard of care." A printable version of this content will be available to control group participants for viewing/printing following completion of the T2 survey. If they wish, control group participants will also have the ability to log back into the portal after the T2 survey to view this content again (see Appendix for Re-accessing Information).

2.f. Out-U Group. The Out-U group will receive the *Outsmart HPV* intervention that includes: a) population-targeted, individually-tailored content via the project website; and b) unidirectional text message/email vaccine reminders (Table 2). This is the intervention from our pilot study.

Population-targeted, individually-tailored content. *Outsmart HPV* content is divided into four sequential sections: "Learn About HPV," "Learn About the Vaccine," "Get Answers," and "Get Vaccinated!" (see Appendix). These sections provide: a) information about HPV and HPV vaccine; b) resources, skills training, and information that address barriers/concerns about HPV vaccine; and c) prompts for men to create a plan for getting vaccinated. Table 2 provides an overview of each section, including the theoretical constructs targeted by each.

Content in the four sections is a combination of text, infographics, and other visual formats. As described below, certain content in these sections is population-targeted (i.e., applies to a population segment[37]) and/or individually-tailored. Targeted/tailored content increases relevance and improves health outcomes.[37-42] A PDF summary of viewed content will be available for printing/emailing (see Appendix). If they wish, participants who receive *Outsmart HPV* will be able to log back into the website after their initial session to review this content (see Appendix for Re-accessing Information).

Table 2. *Outsmart HPV* Intervention Components

Component	Description	Content	Theoretical Constructs*
"Learn about HPV"	• Provides information about HPV & HPV-related diseases (prevalence, risk factors, etc.) • Targeted information for sexual minority men	Targeted	• Vulnerability, severity (PMT) • Information (IMB)
"Learn About the Vaccine"	• Provides information about HPV vaccine (recommendations, vaccine coverage, etc.) • Targeted information for sexual minority men and testimonials for vaccination	Targeted & Tailored	• Response efficacy (PMT) • Information, motivation (IMB)
"Get Answers"	• Provides resources, skills training, and information (including targeted information) that address common barriers/concerns in an order that is tailored to the participant's rankings	Targeted & Tailored	• Rewards, response costs (PMT, IMB, MSM); Self-efficacy (PMT) • Information, skills (IMB)
"Get Vaccinated!"	• Prompts for participants to create a tailored plan that includes when and where to get HPV vaccine and their reasons for wanting to get vaccinated (i.e., motivations)	Tailored	• Self-efficacy, intention (PMT) • Motivation, skills (IMB)
Vaccine reminders	• Monthly text message/email reminders that include information about getting HPV vaccine (unidirectional for the Out-U group and interactive for the Out-I group)	Tailored	• Motivation (IMB) for all; and others for interactive reminders, as needed

**Theoretical framework has aspects of Protection Motivation Theory (PMT), Information-Motivation-Behavioral Skills Model (IMB), and Minority Stress Model (MSM)*

"Learn about HPV" provides information about HPV (prevalence, transmission, etc.) and HPV-related diseases (prevalence, risk factors, etc.). This includes population-targeted information for YSMM (e.g., HPV and HPV-related disease rates among sexual minority men). It is critical to provide this type of information since research has repeatedly shown that many sexual minority men lack knowledge about these topics.[30,45-48]

"Learn about the Vaccine" provides information about HPV vaccine, including recommendations, vaccine effectiveness, and current vaccine coverage estimates. This section includes population-targeted information for YSMM and testimonials illustrating YSMM's motivations for getting vaccinated (based on past work[19,49]).

"Get Answers" addresses common barriers/concerns about getting the HPV vaccine reported in past work among YSMM.[19,45,49-52] Resources, skills training, and/or information are provided to address each barrier/concern. Providing adolescents/young adults with resources and skills training improves health behaviors.[44,53,54]

"Get Vaccinated!" provides prompts for participants to create a tailored HPV vaccination plan of when (i.e., target date) and where to get HPV vaccine and their reasons for wanting to get vaccinated (i.e., motivations). Thus, this section helps participants specify their HPV vaccine implementation intentions, an approach that improves goal achievement and engagement in health behaviors.[59] The resulting tailored HPV vaccination plan is available for printing/emailing (see Appendix for Summary Sheet).

Unidirectional vaccine reminders. Participants in the Out-U group will be sent monthly unidirectional reminders via text message/email about getting HPV vaccine (see Appendix). All

reminders for the Out-U group will be unidirectional, meaning that participants will not have the option to respond to reminders. Reminders will be sent via an automated process linked to the project website. The monthly reminders will start one month after randomization and continue for the 9-month follow-up period, as they can help promote both HPV vaccine initiation and completion.

2.g. Out-I Group. The Out-I group will receive the *Outsmart HPV* intervention that includes: a) population-targeted, individually-tailored content via the project website; and b) interactive text message/email vaccine reminders. The Out-I and Out-U groups will be identical except in the type of vaccine reminders sent to YSMM.

Population-targeted, individually-tailored content. Identical to the Out-U group (see Section 2.f.).

Interactive vaccine reminders. Participants in the Out-I group will be sent monthly tailored interactive reminders via text message/email about getting HPV vaccine (see Appendix). All reminders for the Out-I group will be interactive, meaning that participants will have the option to respond to obtain additional information that is tailored to their individual needs. As with the Out-U group, the monthly reminders will start one month after randomization and continue for the 9-month follow-up period.

Communications for the interactive reminders will be sent through a combination of automated and manual processes, as described further below. To increase participant engagement, some of the interactive reminder texts will also contain a meme or brief animation in Graphics Interchange Format (GIF). Similar to the approach taken in other technology-based interventions with adolescents and young adults,[34] the memes and GIFS are intended to be funny or motivational and reinforce behavior.

For each month, the initial text sent to participants will be automated and include a question that prompts a response. Including a prompted message can increase participant responsivity compared to texts without unprompted messages.[35] Depending on how a participant responds to this initial communication, additional automated communications with information and resources will be sent to participants. Participants will then have the opportunity to text further questions they may have to the study team (participants can ask as many questions as needed). A study team member will review questions received and manually send an appropriate response, based on a library of example responses that has been developed for this study (see Appendix); responses for unanticipated questions will be discussed and agreed upon by the study team.

2.h. T2 Survey. Immediately after viewing intervention or control materials, participants will complete the T2 survey on the project website (about 10 minutes in duration; see Appendix). The T2 survey will assess theoretical constructs and satisfaction with study materials. Participants will not be able to access any study materials during the T2 survey. T2 survey completion will end the initial project website session. Participants will receive a $40 gift card for completing the T1/T2 surveys. Incentives will be sent to participants via email (see Appendix).

If, for some reason, a participant fails to complete all study activities up to this point, they will receive survey completion notifications (see Appendix for Survey Notifications) via email/text message. Survey completion notifications will be sent: 1) immediately after the participant leaves the project website; and 2) 2 days later if study activities have not yet been completed. Participants will have a maximum 3-day window to complete the study activities up to this point. If the 3-day window expires and a participant has not yet been randomized, they will not continue in the study. If the 3-day window expires and a participant has been randomized, they will continue in the study and be offered the opportunity to complete the T3 and T4 surveys.

2.i. T3 & T4 Surveys. Participants will complete the T3 and T4 surveys on the project website at 3 and 9 months after randomization. The T4 survey will occur 9 months later to allow participants ample time to receive all 3 doses of HPV vaccine. The T3 and T4 surveys are included in appendices.

Both the T3 and T4 surveys will take about 10 minutes and assess HPV vaccination status and theoretical constructs. The T4 survey will also assess satisfaction with study vaccine reminders (Out-

U and Out-I groups only). Participants will not be able to access any study materials during the T3 and T4 surveys. Participants will receive a $20 gift card (sent via email) for completing the T3 survey and a $35 gift card (sent via email) for completing the T4 survey (see Appendix).

If, for some reason, a participant fails to complete a survey it has been started, they will receive survey completion notifications (see Appendix for Survey Notifications) via email/text message. Survey completion notifications will be sent: 1) immediately after the participant leaves the project website; and 2) 2 days later if the survey has not yet been completed. Participants will have a maximum 3-day window to complete the survey once it has been started.

To improve retention, the project website will send all participants email/text message notifications to complete each survey (see Appendix for Survey Notifications). For the T3 and T4 surveys, notifications will occur: 1) the day the survey becomes active; 2) 5 days after the initial invite (if the survey has not yet been completed); 3) 8 days after the initial invite (if the survey has not yet been completed); and 4) 11 days after the initial invite (if the survey has not yet been completed). For both the T3 and T4 surveys, participants will have a maximum 14-day window to complete their survey (after which the survey becomes unavailable to complete).

If a participant does not complete the T3 survey in the 14-day window, they will continue in the study and be offered the opportunity to complete the T4 survey. Project website accounts for participants will be deactivated after completion of all study activities or expiration of the 14-day T4 survey completion window (if the T4 survey is not completed).

2.j. Medical Record Release. If a participant indicates he has received HPV vaccine during the T3 or T4 survey, the end of the T3/T4 survey will contain a link to a medical record release form that can be completed online (see Appendix). The form will open in a new window from the project website and be managed using Research Electronic Data Capture (REDCap). REDCap is a software toolset and workflow methodology for electronic collection and management of clinical and research data, to collect and store data. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and variations of data exporting/importing. REDCap is hosted by OSUWMC IT in the Ackerman Datacenter. Participants will have the option of whether or not to complete the MRR form; those who do not will still continue in the study. Completing this form will allow the study team to contact the appropriate healthcare providers to confirm HPV vaccination status.

Following completion of a participant's T4 survey or expiration of the 14-day T4 survey completion window (if the T4 survey is not completed), we will confirm HPV vaccination status via medical records (for those who completed an MRR form). A copy of the signed MRR form along with a request letter from the study team will be presented to a medical facility (via fax, phone, or secure email). The request letter will inform the facility about the study and request information from the medical record about the participant's HPV vaccination history be sent to the study team (via fax, phone, or secure email). Non-responding medical facilities will be contacted again by project staff.

2.k. Online Data Collection and Storage. As mentioned above, data from the MRR will be captured and managed via REDCap. REDCap is hosted by OSUWMC IT in the Ackerman Datacenter, and all data collected via REDCap is secured behind the OSUWMC firewall.

All other online data (e.g., from surveys, etc.) will be collected via the project website and stored by The Center for Health Communications Research (CHCR) at the University of Michigan.[63] CHCR ensures that data collection and storage processes are undertaken with attention to human subjects protections, respect for proprietary data, and maintaining integrity of the source data. CHCR was responsible for data storage and protection during our previous pilot study as well.

To ensure that the data are protected, CHCR uses virtualized servers provided by the University of Michigan Information Technology Services group. The virtualized servers are housed at two

redundant datacenters. These datacenters provide protection from lengthy outages, 24/7 staffing, restricted physical access, and disaster recovery. Virtual servers are backed up automatically onto encrypted tape for recovery and security. The datacenters also reduce the use of physical resources such as electricity and air conditioning.

All servers and the back-end databases are password protected. The server runs the Red Hat Enterprise Linux operating system and security patches and updates are downloaded and installed regularly. Each server is also protected by firewalls to restrict network access to the server. Additional details are available at http://services.it.umich.edu/miserver/.

When a participant accesses the study portal, content will be transmitted securely using a secure socket layer (SSL) protocol, the same protocol used to protect financial and other personal information when transmitted from a web site to a user's browser. This prevents anyone else on the network from intercepting and viewing the content that is being provided to the participant.

Data files that will be sent to the study team will be done so using MiShare, a secure collaborate file exchange system administered by the University of Michigan Health System. The MiShare infrastructure provides a method approved by the UMHS Compliance Office for UMHS personnel, non-UMHS business partners, patients and researchers to securely transfer files, including files that contain electronic Protected Health Information (ePHI), protected research data, or other sensitive information. Files are encrypted while being uploaded or downloaded, and are encrypted while they are on the MiShare server. With MiShare, uploaded packages are not transferred from UMHS systems to external systems. Rather, packages remain on the server and must be retrieved from the UMHS server by the recipient using a provided link. The MiShare system can only be used to transfer files either through SSH/sFTP or through a web https; it is not possible to mount a MiShare volume as a drive letter for a desktop computer. As files are uploaded and bundled in packages, they are also encrypted to allow secure transfer. Packages will only be available for five days. Packages older than 5 days are automatically deleted.

CHCR will also retain a completely de-identified data set to use for quality improvement activities within the Center. No data will be used for the purposes of publication or public presentations without express permission of the project PIs.

2.l. Study Portal Usage Data. For participants in both the intervention and control groups, the project website will capture usage data. These data will include the number of study portal logins during the study, time spent on the project website, and other usage metrics. All of these data will be securely stored using the protections at CHCR described in Section 2.k.

2.m. Sample Size/Data Analyses. We will randomize about 2100 men (700 per arm), expecting 70% retention over the 9-month follow-up (based on our pilot study). We are confident in reaching this sample size given the large number of YSMM on social media and that similar sample sizes have been recruited via social media.[64,65] All analyses will use an intent-to-treat approach.

Aim 1 (Efficacy). We hypothesize HPV vaccine initiation and completion will be higher among participants in both the Out-U and Out-I groups compared to participants in the control group (Hypothesis 1a). Further, we hypothesize that HPV vaccine initiation and completion will be higher among participants in the Out-I group compared to participants in the Out-U group (Hypothesis 1b).

We will first examine descriptive statistics (i.e., proportions and 95% confidence intervals [CIs]). We will then use logistic regression to test our hypotheses, with separate models for HPV vaccine initiation and completion. Models will control for any potential confounders (i.e., variables that differ between study arms [$p<0.10$] at baseline). For each outcome, we will perform all pairwise comparisons of study arms, using a Bonferroni corrected two-sided alpha of 0.017 to control the overall type I error rate. We will have at least 80% power for all comparisons,[66] assuming our

projections of initiation (control=20%; Out-U=35%; Out-I=45%) and completion (control=10%; Out-U=22%; Out-I=35%). Projections are based on pilot study results and past work on different types of reminders.[67,68] Logistic regression models will produce odds ratios (ORs) and 95% CIs. Results will determine the efficacy of *Outsmart HPV* and identify which type of HPV vaccine reminder most effectively increases vaccination.

Aim 2 (Mediation). We will examine all theoretical constructs as potential mediators (see Section 2.n.). We hypothesize the effects of the intervention will be mediated by changes in theoretical constructs, including increased perceived vulnerability to HPV and HPV-related disease, reduced response costs of getting HPV vaccine (e.g., reduced concerns about vaccine safety and side effects), increased self-efficacy to get HPV vaccine, and increased intention to get HPV vaccine (Hypothesis 2). This hypothesis is based on our pilot study results, where *Outsmart HPV* caused larger changes in each of these constructs than the control group.[69] We expect mediators will be similar for both HPV vaccine initiation and completion.

To test this hypothesis and identify mediators, we will use structural equation modelling (SEM). SEM has several advantages over standard regression analyses, including the ability to assess multiple potential pathways in one model.[70] We will examine HPV vaccine initiation and completion separately and use a probit link to transform each binary outcome to a standard Normal scale.[70] For each outcome, we will fit two models using a maximum likelihood approach: a "full" model and a more parsimonious "final" model. The "full" model will include study arm, all theoretical constructs, and an outcome variable. We will examine the overall model fit of the "full" model via the Root Mean Square Error of Approximation (RMSEA) and other metrics (chi-square test, etc.).[71,72] We will consider a RMSEA<0.07 to indicate acceptable fit.[72] To create the "final" model, we will remove pathways (i.e., associations) from the "full" model based on effect size and the chi-square test for nested models. This process will continue until removing pathways no longer improves the model. The resulting model will be the "final" model. SEM models will produce standardized path coefficients that estimate the direct and indirect effects of study arm and the theoretical constructs. Given our analytic sample size, we will have at least 90% power to rule out RMSEA≥0.08 with 95% confidence. Results will identify which changes in theoretical constructs are the key drivers of *Outsmart HPV* increasing HPV vaccination.

Aim 3 (Moderation). We will examine demographic and health-related characteristics from the screener and T1 surveys as potential moderators. We hypothesize intervention effects will be stronger (i.e., moderation) among YSMM who are not married or in a relationship (due to higher perceived vulnerability to HPV and HPV-related disease), live in urban areas (due to greater access to care, including LGBT-friendly providers), report having a routine medical check-up in the last year (due to higher utilization of healthcare and self-efficacy to get HPV vaccine), or report having disclosed their sexual orientation to a healthcare provider (due to higher self-efficacy to talk with a healthcare provider about HPV vaccine) (Hypothesis 3). We expect moderators will be similar for both HPV vaccine initiation and completion (which will be examined as separate outcomes).

We will use logistic regression models that include an interaction term between each potential moderator and study arm to test this hypothesis and identify moderators. Logistic regression models will produce ORs and 95% CIs. We will consider an interaction present if an interaction term has p<0.05. Given our analytic sample size, we will have 80% power to detect interaction terms with ORs≥2.30. Results will determine if intervention efficacy differs by demographic and health-related characteristics.

2.n. Potential Challenges. Recruitment: We have expertise recruiting YSMM via social media[26,44,73-77] and will offer study incentives. **Retention:** We expect 70% retention based on our pilot study and will provide incentives and survey notifications to aid retention. **Missing data:** Missing survey data will be minimized by using prompts for skipped items. This resulted in less than 5% missing data in our pilot study. **Outcome ascertainment:** HPV vaccination status will be confirmed by medical records if MRR is provided, otherwise self-reported data will be used. **Generalizability:** To maximize

generalizability, participants will be recruited throughout the US. YSMM recruited via Facebook in our pilot study were demographically similar to YSMM from nationally representative samples.[26-28] **Contamination:** We do not expect contamination since we will recruit throughout the US, the project website will require login, and participants will receive only the study materials for their randomized study arm.

2.o. Project Timeline (Table 3). The timeline is based on our past work on RCTs and interventions.[44,61,62,69,78-86]

Table 3. Project Timeline

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Randomized trial												
Recruitment	●	●	●	●	●							
Data collection	●	●	●	●	●	●	●	●	●	●		
Data mgmt. / analyses	●	●	●	●	●	●	●	●	●	●	●	●
Manuscript writing					●	●	●	●	●	●	●	●

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

1.a. Human Subjects Involvement and Characteristics. During the RCT, we will randomize 2100 YSMM. Eligibility criteria will include: a) cisgender male; b) ages 18-25; c) sexual minority (reports ever having oral or anal sex with a male or being sexually attracted to males; or identifies as gay, bisexual, or queer); d) lives in the US; e) has not received any doses of HPV vaccine; and f) did not participate in the pilot study. We will require men to read English and able to provide informed consent (inferred by completing the screener survey and consent form). Participants will be randomized to either: a) standard information about HPV and HPV vaccine via a mobile-friendly website (control group); b) *Outsmart HPV* with unidirectional vaccine reminders (Out-U group); or c) *Outsmart HPV* with interactive vaccine reminders (Out-I group). Participants will complete four online surveys over a nine-month period. All online surveys will be self-administered.

1.b. Sources of Materials. Research materials for this project will be obtained through online surveys and medical record review (if medical record release is provided) for the RCT. All data will be collected in a standardized manner in an effort to protect the validity and integrity of the research project. Only members of the study team will have access to the collected information.

1.c. Potential Risks. We believe this research will present minimal risk to human subjects. We do not anticipate any psychosocial harm, economic harm, legal jeopardy, or other side effects for participants in the RCT. There is the small possibility that some RCT participants may find some of the survey topics embarrassing or worrisome. However, surveys of this type are routinely conducted, with no ill effects to participants. Because surveys will be completed online in participants' homes (or elsewhere if they prefer) with the option to not complete each survey, we feel that this is a minimal risk. The instructions for the study surveys will clearly indicate that participants do not have to answer any questions that they do not want to answer. All communications for vaccine reminders (Out-U and Out-I groups only) will be sent via text message/email. We do not anticipate that any of these communications will contain information that would cause any psychosocial harm, economic harm, legal jeopardy, or other side effects. All reasonable efforts will be made to ensure the emotional safety and well-being of each participant. However closely monitored, there may be risk associated with loss of confidentiality of information. Lastly, there could be unlikely circumstances when the study team may need to breach confidentiality (e.g., if for medical reasons, as required by law, etc.).

2. Adequacy of Protection Against Risks

2.a. Recruitment and Informed Consent Procedures. During the RCT, we will randomize about 2100 YSMM who will be recruited from social media sites, existing online panels (e.g., Amazon Mechanical Turk), and through professional contacts (e.g., co-investigators distributing approved social media advertisements). Eligibility criteria will include: a) cisgender male; b) ages 18-25; c)

sexual minority (reports ever having oral or anal sex with a male or being sexually attracted to males; or identifies as gay, bisexual, or queer); d) lives in the US; e) has not received any doses of HPV vaccine; and f) did not participate in the pilot study. We will require men to read English and able to provide informed consent (inferred by completing the screener survey and consent form). All men will provide informed consent to participate in the RCT. The project website will provide participants with detailed information about the study prior to consent. For the RCT, participants will also be asked to provide medical record release (MRR), allowing for confirmation of HPV vaccination status during the study. The MRR form will be accessed through the project website and be managed using Research Electronic Data Capture (REDCap). A completed MRR form will not be required for study continuation.

2.b. Protection Against Potential Risk(s). Every means will be taken to minimize the risk associated with participating in this project. The autonomy of participants will be protected by informing all participants of the purpose of the study and allowing them to opt out of participation without repercussion. Participants will be able to withdraw from the study at any time, and they will be able to refuse to answer any question. Participants will be provided with study contact information in case they have any questions or concerns or experience any negative outcomes.

Several precautions will be taken to avoid any breach of confidentiality. Participant ID numbers will be used instead of names of participants on study-related documents and in the study databases. The ID numbers and names will be linked to a master list that will be accessible only to the study team. The master list will be kept in a computerized tracking system that will be password protected behind a firewall. All electronic files and databases will be kept on a password protected computer accessible only to study team members behind a firewall. This includes de-identified datasets. All paper-based study forms will be stored in locked file cabinets that are only accessible to study team members. For participants in the Out-I group, communications for the interactive vaccine reminder process will not include any confidential information. All study team members will complete National Institutes of Health (NIH) and institutional requirements in training for responsible research and the ethical treatment of human subjects. Documentation of completion of training will be maintained on file. If for medical reasons or as required by law, the study team may have to breach confidentiality.

3. Potential Benefits of the Research to Human Subjects and Others

There may or may not be direct benefits to the participants of this study. Potential benefits to the participants will come in the form of improved HPV vaccination knowledge and behaviors. The information learned from this study may benefit sexual minority men in the future. The participants and society in general will benefit from this study to the extent that the results improve our understanding strategies to improve HPV vaccination among sexual minority men. The benefits far outweigh the risks of this study, since the possible risks are minimal and because the possible benefit is so great.

4. Importance of the Knowledge to be Gained

Sexual minority men have high rates of HPV infection and HPV-related disease, and therefore YSMM can benefit greatly from HPV vaccination. We recently developed and pilot tested *Outsmart HPV*, the first HPV vaccine intervention for YSMM that we are aware of. This study is the necessary next step in this line of research and will comprehensively evaluate the *Outsmart HPV* intervention. In doing so, it will provide an evidence base regarding the intervention's efficacy (including what type of HPV vaccine reminders are most effective for the intervention), mediators, and moderators. We will make every effort to present findings at scientific meetings and to publish findings in peer-reviewed journals.

5. Data and Safety Monitoring Plan

We have developed a Data and Safety Monitoring Plan for this study. The purpose of the data and safety monitoring plan is to ensure the safety of participants, the validity and integrity of data, and the

appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the study cannot be concluded successfully. Risks associated with participation in research must be minimized to the extent practical and the method and degree of monitoring should be commensurate with risk. The essential elements of the Data and Safety Monitoring Plan include: a) monitoring the progress of the study and the safety of participants; b) plans for assuring compliance with requirements regarding the reporting of adverse events; c) plans for assuring that any action resulting in a temporary or permanent suspension of the study is reported to the appropriate agencies; and d) plans for assuring data accuracy and protocol compliance.

Prior to the initiation of the project, all study team members will receive standardized training to ensure that the activities of the study are conducted in a uniform, safe, confidential, and secure manner. The project website contains an administrative console that will allow the study team to document and monitor study activities (e.g., recruitment, data collection, etc.). Study team meetings will take place on a monthly basis to monitor study activities and to continually reassess the progress of the study, including assessments of data quality, timeliness, participant recruitment, accrual, retention, protocol compliance, and monitoring of the risk versus benefits throughout the study period.

All adverse events will be reported according to the policy outlined by the IRB at OSU. The appropriate forms will be completed and sent in accordance to the timeline set forth by the IRB. All adverse events will be reported to and reviewed by the study team. All protocol violations will be documented and reported to the IRB. Also, any privacy violations will be reported to the IRB and the institutional privacy offices. All privacy violations, adverse events, and protocol violations will be reviewed by the multi-PIs (Drs. Paul Reiter and Annie-Laurie McRee) and the rest of the study team. Dr. Reiter will be responsible for reporting to the OSU Office of Responsible Research Practices/IRB and the NIH project officer. The IRB will be provided feedback more frequently if there should be any adverse events or other recommendations. Dr. Reiter will also be responsible for reporting to the NIH project officer any action resulting in temporary or permanent suspension of the research project at OSU. These actions must be reported to the NIH project officer within 72 hours of notification. All documents or correspondence that are generated in the course of correcting or appealing the suspension status must also be forwarded to the project officer within 72 hours of it being presented to the institutional body that put forth directive to temporarily or permanently suspend the research project. During this time, no research project activities can occur.

Dr. Reiter will be responsible for submitting reports, including annual reports to the OSU IRB and the NIH. Information included in the reports will include the number of individuals enrolled in the study, dropout rates, and any protocol deviations.

6. ClinicalTrials.gov and Good Clinical Practice (GCP) Training

This study will involve a randomized controlled trial of an HPV vaccine intervention for YSMM. Therefore, it will be registered in ClincialTrials.gov. Throughout the ClincialTrials.gov process, we will adhere to the policy recently released by the NIH. Specifically, we will: a) ensure registration to ClincialTrials.gov occurs no later than 21 days after the first participant is enrolled into the randomized controlled trial; b) submit all required information during the registration process (descriptive, recruitment, location/contact, and administrative information); c) ensure results information is submitted no later than one year after the primary completion date of the randomized controlled trial; d) submit all required information during results reporting (participant flow information, demographics and baseline characteristics of enrolled participants, primary and secondary outcomes including results of any scientifically appropriate statistical tests, and adverse events); and e) update all submitted information once a year. Related, study team members will complete training in Good Clinical Practice (GCP) regarding clinical trials, as appropriate. This expectation was established by a recent policy statement from the NIH.

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