Official Study Title: Improving the Reach & Effectiveness of Smoking Cessation Services Targeted to Veterans Living With HIV

NCT Number: NCT04505371

Date of Most Recent IRB Approval: 8/12/2024

Documents included:

- Study Protocol
- Statistical Analysis Plan
- Informed Consent Form

Human Subjects Protocol

VA Puget Sound IRB

Improving the Reach and Effectiveness of Smoking Cessation Services Targeted to Veterans Living with HIV

[MIRB # 01818]

Funding Agency: National Cancer Institute

Principal Investigator: Kristina Crothers, MD

Current Version: July 29, 2024

Abstract

Tobacco use remains the leading preventable cause of death and illness in our society, and smoking rates are disproportionately high among people living with HIV. Research suggests SLWH are largely unaware of the HIV-specific deleterious effects of smoking and often lack motivation and confidence in their ability to quit. For these reasons, we developed the Wellness Intervention for Smokers with HIV (WISH). WISH is grounded in the Information-Motivation-Behavioral Skills (IMB) Model and delivered remotely by mobile phone (voice and text message). The program is designed for *all* SLWH, regardless of their initial motivation to quit. WISH follows evidence-based, best practice guidelines for nicotine dependence treatment, but is innovative in its use of a more comprehensive wellness approach. That is, the intervention addresses both smoking and a number of other personally relevant health behaviors (such as treatment adherence, stress/mood, nutrition, other substance use, etc.), making it relevant and engaging to all SLWH, not just those ready to stop smoking. For those not yet ready to quit, WISH is designed to build and strengthen motivation and self-efficacy for quitting, while smokers also work on other personal health goals. Once ready to quit smoking, participants receive evidence-based cognitive-behavioral counseling and encouragement to use nicotine replacement therapy (NRT) or other appropriate pharmacotherapy. WISH builds on our extensive experience creating motivationally-enhanced cessation interventions and has been pilot tested with SLWH. In this trial, we will compare the effectiveness of WISH to standard care services offered through the National VA Quitline and the SmokefreeVET texting program, NCI-supported tobacco cessation services available to all Veterans. Participants in both arms can receive phone/ text counseling and have access to pharmacotherapy through VA. Primary outcomes will be 7-day point prevalence smoking abstinence and presence of any 24-hour intentional quit attempts. Secondary outcomes will include prolonged abstinence, change in cigarettes per day, intermediate change process outcomes based on the IMB model, as well as metrics of intervention reach and implementation. We will also describe comorbidities and explore intervention impact on markers of immune status and mortality risk using the outstanding clinical data resources available through the Veterans Aging Cohort Study (VACS). If effective, WISH could meaningfully reduce smoking among HIV+ Veterans nationwide. To support this goal, dissemination efforts are planned in Year 5 to share the WISH program with the National VA Quitline. Because VA is the largest U.S. provider of HIV care, this research has the potential for significant public health impact.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

- Acquired Immunodeficiency Syndrome (AIDS)
- Agency for Healthcare Research and Quality (AHRQ)
- American Thoracic Society (ATS)
- Antiretroviral therapy (ART)
- Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)
- Body mass index (BMI)
- Behavioral Risk Factor Surveillance System (BRFSS)
- Cardiovascular disease (CVD)
- Cardiovascular risk factors (CVRFs)
- Centers for Disease Control and Prevention (CDC)
- Centers for Medicare and Medicaid Services (CMS)
- Chronic obstructive Pulmonary Disease (COPD)
- Cluster of differentiation 4 (CD4)
- Data Safety Monitoring Board (DSMB)
- Drug Abuse Screening Test (DAST)
- Electronic health record (EHR)
- Food and Drug Administration (FDA)
- Generalized estimating equations (GEE)
- Health Insurance Portability and Accountability Act of 1996 (HIPAA)
- Human Immuno-deficiency Virus (HIV)
- Human papillomavirus (HPV)
- Information-Motivation-Behavioral Skills (IMB)
- Institutional Review Board (IRB)
- Kaiser Permanente Washington Health Research Institute (KPWHRI)
- National Institutes of Health (NIH)
- National Cancer Institute (NCI)
- Nicotine replacement therapy (NRT)
- Office of Behavioral and Social Sciences Research (OBSSR)
- Patient Health Questionnaire (PHQ)
- Point prevalence abstinence (PPA)
- Protected Health Information (PHI)
- Principal Investigator (PI)
- Randomized Controlled Trial (RCT)
- Research and Development (R&D)
- Research Electronic Data Capture (REDCap)
- Ribonucleic acid (RNA)
- Smokers Living with HIV (SLWH)
- Standard Care (SC)
- Transport Layer Security (TLS)
- University of California Davis (UCD)
- University of Washington (UW)
- United States Preventive Services Task Force (USPSTF)
- Veterans Affairs (VA)
- Veterans Aging Cohort Study (VACS)
- Wellness Intervention for Smokers with HIV (WISH)

Contents

Protocol Title:.....5
1.0 Study Personnel.....5
2.0 Introduction.....5
3.0 Objectives.....5
4.0 Resources and Personnel.....5
5.0 Study Procedures.....6
5.1 Study Design.....6
5.2 Recruitment Methods.....6
5.3 Informed Consent Procedures.....7
5.4 Inclusion/Exclusion Criteria.....7
5.5 Study Evaluations.....7
5.6 Data Analysis.....7
5.7 Withdrawal of Subjects.....7
6.0 Reporting.....8
7.0 Privacy and Confidentiality.....8
8.0 Communication Plan.....8
9.0 Information Security and Data Storage/Movement.....9
10.0 References..... .9

Protocol Title: Improving the Reach and Effectiveness of Smoking Cessation Services Targeted to Veterans Living with HIV

1.0 Study Personnel

Principal Investigator:
- Kristina A. Crothers, MD, 206-277-3013, Kristina.Crothers@va.gov

Co-Investigators:
- Emily C. Williams, PhD, MPH, (206) 277-6133, Emily.Williams3@va.gov

Collaborators (at other institutions, not covered under the VA IRB approval):
- Jennifer B. McClure, Jennifer.B.Mcclure@kp.org
- Sheryl L. Catz, scatz@ucdavis.edu
- Jaimee Heffner, jheffner@fredhutch.org
- Kathleen Akgün, Kathleen.akgun@va.gov
- Benjamin Balderson, Benjamin.H.Balderson@kp.org

2.0 Introduction

SIGNIFICANCE AND SCIENTIFIC PREMISE.
Smoking is a leading preventable cause of death and illness[1], including among people living with HIV (PLWH). Smoking rates are exceptionally high among PLWH, often 2-3 times higher compared to the general population[2-14] and the deleterious effects of smoking are compounded among PLWH who smoke, contributing to health disparities. The most common non-HIV-related causes of death include the tobacco-related conditions of cardiovascular and pulmonary disease, non-HIV-related cancer (most of which are directly related to tobacco use), as well as liver disease, alcohol and other substance use and disorders[15-21]. In recognition of this shift, the Infectious Diseases Society of America recommended that health care for PLWH expand from a primary focus on HIV-related illnesses to include other preventable conditions[22]. We and others have shown that smoking is associated with reduced quality of life, increased risk of bacterial pneumonia and other AIDS defining illnesses, lung cancer and other malignancies, and two-fold greater mortality for PLWH who smoke compared to those who do not[3-5,14,20,23-28]. Smoking is also the most significant modifiable risk factor for many non-AIDS defining chronic conditions, including cardiovascular disease and chronic lung disease[17,18,28-32]. Notably, smokers may have poorer viral and immunologic responses to antiretroviral therapy (ART) and higher risk of developing AIDS[15,23,33,34] . *In sum, smoking cessation is critically important to improve health in PLWH.*

Calls for research and limited evidence base. In recognition of the health disparities caused by smoking among PLWH, NIH and others have called for more research to inform the effective treatment of smoking in this high-risk population[13,35-45]. *The proposed research is responsive to this call.* Amazingly, a 2014 systematic review found that only 5 published RCTs had tested cessation treatment among SLWH[46] and a 2016 literature synthesis characterized the cessation literature for SLWH as sparse and with mixed efficacy findings[47]. As a result, the empirical evidence base to inform how best to promote cessation in this high-risk population is limited. Standard care smoking cessation services appear inadequate to address the needs of SLWH given that smoking rates remain so *exceptionally high* among SLWH compared the general population.[1,7,12,43]

Moreover, the limited evidence to date does not support a standard-care approach with SLWH; a recent Cochrane review showed pooled long-term abstinence of standard care controls was 8% among 6 studies conducted with SLWH[48].

Review of prior studies: A case for a *new* type of evidence-based intervention strategy. Studies that have tested standard care (i.e., cessation counseling + pharmacotherapy) or some version of this among SLWH failed to find that traditional enhancements to this strategy were sufficiently effective[48]. For example, in a single arm longitudinal study where 247 SLWH were given an intensive best practice cessation intervention (12 weeks of cognitive behavioral telephone counseling + varenicline or nicotine replacement therapy [NRT]), cotinine-confirmed abstinence was only 10% at 12 months.[42] An intervention comparing standard care advice to quit + NRT to 8-session tailored group therapy among 145 SLWH did not find significant differences between the arms even at an immediate post assessment point of 3 months (9.2% versus 19.2%)[49] and an online cessation program compared to usual care advice also found low rates in both arms overall (10% vs. 4%) with abstinence reaching 18% only among those completing all 8 online sessions[50]. In one of the largest trials conducted with SLWH (n=444), participants were randomized to 2 brief sessions of in-person standard care + self-help + NRT or 4 sessions of in-person motivational interviewing + NRT. Smoking abstinence rates at 6 months were equivalent in each arm (9-10%), suggesting that cessation-focused in-person strategies were not an effective way to enhance motivation in SLWH[51], and that more innovative or comprehensive strategies are warranted. Importantly, the cessation rates in these studies are well below the long-term quit rates observed in non-HIV populations provided phone counseling + pharmacotherapy (abstinence range 24% - 32%)[35]. Some of the most promising studies with SLWH come from remotely-delivered interventions, improving reach[52]. For example, Gritz et al.[39] found urban SLWH offered cell phone counseling were 2.4 times more likely to quit than people receiving usual care (P = .049), and Humfleet et al.[38] reported 7 day PPA rates of 27% at 6 months among SLWH who received a computer-based intervention + NRT. Thus, there is good reason to believe that remotely delivered counseling interventions will be more effective than "standard care" interventions with SLWH, particularly if smokers remain engaged in the program, but overcoming barriers to access alone will not be sufficient to enhance cessation rates. *We contend that for interventions to be more effective with SLWH, they need to utilize more appealing or comprehensive strategies to overcome traditional barriers to care, and their content also needs to be adapted and tailored to meet the unique needs and interests of SLWH. Moreover, programs need to cast a broad net and not be limited to those ready to quit*, as explained below.

Enhancement to standard care #1: Intervene with smokers, regardless of readiness to quit. It is well documented that most smokers want to quit someday, but at any given time, only ~ 20% or less are ready to quit smoking in the next month[53-57]. This holds true among SLWH. We found that 21.5% of SLWH surveyed were in the Preparation stage (ready to quit smoking in the next month), whereas 68% were in the Contemplation stage (thinking about quitting in the next 6 months, but not next month)[58]. We call this latter group "ambivalent" smokers. Most "standard care" interventions are only designed for those smokers who are ready to take action to quit, not those who are ambivalent. *This is a significant treatment gap*, especially because research has shown that ambivalent smokers are interested in receiving intervention services and will reduce their smoking levels in response to intervention.[59] In our prior work, we found ambivalent smokers are willing to enroll in clinical trials when it is clear that the goal is to help them explore their willingness to quit or to answer questions about the quitting process, as opposed to asking for a commitment to stop smoking; many even successfully quit.[60,61] Others have shown that setting a goal of smoking reduction increases quit rates among ambivalent smokers, particularly when counseling is paired with a stop-smoking medication[62-66]. *Thus, there is good reason to expect interventions targeting ambivalent smokers can be effective, particularly if they are*

designed to be sensitive to smokers' ambivalence. Fagerstrom suggests ambivalent smokers require softer, more gradual intervention approaches, even if they contain some of the same basic behavioral and pharmacological strategies that are effective with smokers who are ready to quit.[67] This recommendation is consistent with West's PRIME theory of motivation, which suggests motivation and stage of change are highly fluid and change quickly over time.[68] As a result, West argues there is no reason to exclude ambivalent smokers from treatment; rather, we need to modify interventions to be more engaging to them, in addition to those ready to quit. *This is the goal of the proposed intervention*.

Intervening with smokers, regardless of their readiness to quit, is a paradigm shift that could be an important tactic for reducing smoking, particularly among vulnerable smokers such as Veterans and PLWH. This approach has been demonstrated to be effective among low socioeconomic status (SES) smokers at all levels of readiness to quit in both general population and Veteran-only samples. Work conducted by Fu et al., which specifically focused on proactive outreach to low SES smokers in both VA and non-VA settings, showed a 30-50% increase in the odds of quitting at 1-year post-intervention as well as 6 times higher odds of using evidence-based tobacco treatment[69]. Such findings support our general research premise that targeting smokers at VA, regardless of their readiness to quit, may be an effective way to improve the reach and effectiveness of cessation treatment among SLWH. However, for these interventions to be effective, they must be able to both motivate smokers to want to quit and support their cessation efforts. Effective motivational treatments are generally lacking in this population[70] and more research in this area has been called for[35]. In fact, almost all research among SLWH to date has focused on those ready to quit, or has used relatively brief interventions that yielded low 6-month abstinence rates among those not committed to quit (9-10%)[51], suggesting that more intense or comprehensive intervention may be needed in this population. *We hypothesize it is necessary to not only provide motivational counseling and medication access, but also cognitive-behavioral skills-based counseling, HIV-specific smoking cessation education, and relatively intensive contact to effectively intervene with SLWH. Additionally, to fully engage SLWH who are not ready to quit smoking, it may be important to integrate the counseling in a broader wellness-based intervention*.

Enhancement to standard care #2: Integrate smoking cessation into a comprehensive wellness-based approach tailored to PLWH. SLWH require interventions designed to meet their unique treatment needs[36,71]. Quitting in this population may be complicated by high rates of depression and other substance use[58,72], both of which are common in this community and known to make cessation more difficult[71,73,74]. Moreover, many people are unaware how HIV and tobacco use interact to put their health at risk, and some may have low motivation or lack the skills to add smoking reduction to their already extensive HIV self-care activities[, 6,58,75-77]. SLWH may perceive HIV as their only health concern and many perceive strong coping benefits to smoking, with few perceived risks[58,77-79]. Others perceive smoking cessation as another burden, similar to medication adherence, but much less important[76]. Interventions targeted to SLWH must address these issues. To address the unique needs of SLWH, we developed and piloted an intervention called WISH (Wellness Intervention for Smokers with HIV, see also Preliminary Studies). WISH builds on our prior research in motivational treatment for smoking cessation[80-82] and health behavior change among PLWH[83-90]. WISH incorporates best practice, evidence-based behavioral counseling for smoking cessation with strategies from motivational interviewing[71,91] and is delivered via phone with integrated text messaging. Participants are also encouraged to use cessation medication and advised how to do so. The goal of the intervention is to build and strengthen smokers' motivation for quitting (if not yet ready to quit) and once they are ready, to offer best practice action oriented counseling and pharmacotherapy. But, ***to engage and retain smokers, the program is designed as a wellness intervention***, not a traditional smoking

cessation program. After clarifying smokers' goals around their health and wellness, the program works with SLWH to address these goals through a multi-faceted focus on multiple (inter-related) topics relevant to their health goals, including smoking cessation, treatment adherence, mood management, substance use, etc. This approach is consistent with some of the most recent intervention development work with SLWH that addresses depressed mood in tandem with smoking cessation[92,93] or addresses medication adherence[94], but the WISH approach is relatively broader as it is based on a chronic disease wellness framed self-management approach with demonstrated acceptability among PLWH, including when delivered by phone[95-99].

Enhancement to standard care #3: Integrated phone and text counseling. Finally, WISH is delivered via mobile phone, to reduce many of the traditional barriers to care. Both phone counseling[71,100,101] and more automated or reminder-focused text messaging approaches[102,103] have been demonstrated as effective independent intervention strategies among the general smoking population, have been used to target ART adherence in other HIV populations[104,105], and mobile-phone counseling alone has been used to target SLWH who are ready to quit in the next 7 days[106]. However, *WISH is novel in using integrated text messaging as a way to foster ongoing supportive action-oriented and motivational communications between smokers and telephone counselors in between counseling sessions*. A recent study combining phone and text in a cessation program for SLWH offered the two modes in tandem, but the texts were not customized, bidirectional or integrated with phone counseling as WISH text are, and so did not independently improve cessation beyond the effect of telephone counseling[94]. Moreover, smartphone-based cessation treatments for SLWH can be feasible and engaging when offered to low SES populations, as was recently demonstrated in a feasibility/acceptability pilot with 100 men and women (81% Black; 31% Latino) drawn from a poor urban community[107]. Given the high penetration of mobile phones globally[108], particularly among lower income demographic groups, this intervention modality is particularly well suited for our geographically dispersed target population of HIV+ Veterans, and if successful, appropriate for potential adoption by existing providers of national cessation services available to VA patients.

INNOVATION & IMPACT

This research has several innovative aspects that strengthen potential impact. First, it aims to evaluate a comprehensive, motivational wellness-based intervention for SLWH that is applicable to all smokers, not just those ready to quit. There are few large trials evaluating motivational interventions that include smokers who are ambivalent about quitting smoking, and studies conducted with SLWH are particularly lacking[51,109]. Reaching and engaging these patients in evidence-based cessation treatment has great potential for reducing disparities in care and health outcomes. Second, the study is innovative in its use of a wellness-based approach based on an Information-Motivation-Behavioral Skills Model of Smoking Cessation that our team articulated specifically for HIV+ smokers[110]. The IMB model was developed to guide HIV-related health behavior changes including prevention, adherence and engagement and in one recent study was applied to medication adherence among SLWH, but our team was the first to apply it to smoking cessation and quit attempts as the primary targets[58,83,88,94,110,111]. Third, we propose a novel approach to evaluation, applying the RE-AIM model[112] to examine the role of comorbidities and co-infections on the reach, effectiveness, adoption and implementation of an HIV smoking cessation intervention, leveraging uniquely strong and available VA clinical and health services data to do so. Our collaboration with the National VA Quitline to potentially disseminate the WISH intervention, as appropriate based on final results, is also a unique strength of the proposed project. Fourth, this study will be the first to use the VACS Index 2.0[113]to explore the impact of a smoking cessation intervention on reducing mortality risk for PLWH. This index includes expanded clinical metrics that may be particularly relevant for evaluating smokers. Fifth, we will leverage collaborations with VACS nationally and enroll PLWH receiving care in the VA

system who currently smoke. These Veterans represent a high-risk population who are predominantly black, of lower socioeconomic and educational status, and have multimorbidity and increased mortality risk compared to HIV+ non-smokers. They often have a long-standing history of smoking, high levels of addiction, and are vulnerable to the negative health consequences of ongoing smoking. New interventions to decrease smoking in this population are urgently needed and can have significant impact to improve health. In sum, this research addresses an **important public health need** and is **highly responsive** to NIH goals of reducing smoking and health disparities among SLWH. If found effective, the **innovative** WISH intervention could have a meaningful **impact** on treatment for SLWH served by the largest provider of HIV care in the US and could represent a new model for intervening with SLWH.

3.0 Objectives

Health disparities persist for smokers living with HIV (SLWH) relative to other smokers or to non-smokers living with HIV. People living with HIV smoke at more than twice the rate of the general population and have lower rates of cessation[12,114]. Disparities in health outcomes for SLWH include decreased immunological and viral responses to antiretroviral therapy (ART)[15,33,34,115], increased risk of non-AIDS-related cancers, infections, comorbidities and mortality[2,4,17,18,20,23-27,29,31,32,116-119]. Thus, *it is critical that SLWH quit smoking*. However, research by our team and others has shown that SLWH are largely unaware of these HIV-specific deleterious effects of smoking[40,58,110]. Additionally, our work in the Veterans Aging Cohort Study (VACS) demonstrated that Infectious Disease providers were less likely to be aware of HIV+ patients' smoking or refer them to treatment compared to general medical clinic providers[120]. While this may be in part related to few SLWH being ready to quit at any given time, interest in quitting among many SLWH is high; we have found about 70% would like to quit someday[58,72]. Unfortunately, standard care cessation services are not appealing to SLWH who are not yet ready to quit. Interventions need to be designed to enhance motivation and self-efficacy for quitting, as well as provide the support, advice, and treatment necessary for a successful quit attempt. SLWH also have other needs that may make standard care cessation services less effective[13]. For example, many SLWH have high levels of comorbid depression and substance use[40,121], particularly Veterans[72]. Cessation programs for SLWH also need to be tailored to address these needs.

We previously developed a motivational intervention targeted to SLWH called WISH (Wellness Intervention for Smokers with HIV)[122]. WISH combines HIV-specific information and skills building exercises to enhance and support smokers' motivation and self-efficacy for quitting. The counseling is designed for people at all stages of readiness to quit, not just those ready to make a quit attempt. WISH utilizes best-practice strategies from motivational interviewing and cognitive behavioral counseling[71]. To engage smokers, the program uses a comprehensive wellness approach, focusing on a range of behaviors including medication adherence, mood/stress management, other substance use and health behaviors. Once individuals are willing to make a quit attempt, they are offered action-oriented counseling. Participants are also encouraged to use first-line pharmacotherapy available through Veterans Affairs (VA) health care providers. Unlike most standard care, the program improves reach by not requiring a commitment to quit as a precondition of enrollment. This approach has been well accepted in our prior research with SLWH and others[61,81,82,122-124]. The WISH program content and tone were informed by a series of formative studies we conducted with smokers living with HIV, depressed smokers, and smokers recruited from a range of community and healthcare delivery settings[58,80,110,122,125]. Preliminary findings have all been positive and support broader testing of this approach in the proposed randomized controlled trial (RCT). We will enroll SLWH at VACS

sites, leveraging our existing research infrastructure and access to a large racially and geographically diverse sample with comprehensive data on health outcomes to achieve the following **specific aims:**

1. Compare the effectiveness of WISH (an HIV-specific comprehensive wellness program designed to offer integrated phone & text counseling regardless of readiness to quit) to referral to standard evidence-based cessation services (National VA Quitline and SmokefreeVET texting program). Smokers in both arms will be encouraged to use pharmacotherapy and have access to this via the VA pharmacy. We will conduct an RCT to test the hypothesis that 7-day point prevalence abstinence (PPA) at 6 months and presence of any 24-hour intentional quit attempt (primary outcomes), and self-reported prolonged abstinence, 7-day PPA, 30-day PPA, and change in cigarettes per day at 3 and 6 months post-randomization (secondary cessation outcomes) will be higher in WISH compared to the standard care arm. [Primary aim]

2. Describe the reach and implementation of WISH. We will assess the absolute number, proportion and representativeness (in terms of current readiness to quit, smoking history and demographic characteristics, ART use, comorbidities such as non-AIDS defining cancers, and HIV-related co-infections) of SLWH who are willing versus unwilling to enroll in the program, who do or do not use standard VA cessation services, and who use or do not use cessation medications during the study period. [Secondary aim] There are no hypotheses; this is a descriptive aim.

3. Compare cognitive-behavioral change process variables between WISH and standard care arms at 3 and 6 month follow-up. Variables will be based on the Information-Motivation-Behavioral Skills Model for Smoking Cessation (i.e., HIV specific smoking-related knowledge, motivation and self-efficacy for quitting, and cessation-related behavioral skills including cessation medication use and adherence) [Secondary aim] There are no hypotheses; this is a descriptive aim.

4. Compare markers of immune status (CD4 cell count) and mortality risk (VACS Index) between WISH and standard care at 6 and 12 months. [Secondary aim] We hypothesize that the CD4 cell counts and VACS Index scores will be improved at 12 months in the intervention patients.

If successful, this theory-based program tested with Veterans receiving care from the largest US provider of HIV services could impact reach and effectiveness of cessation services offered to all PLWH regardless of readiness to quit, reduce HIV-related disparities in smoking, and improve clinical outcomes.

4.0 Resources and Personnel

Recruitment and oral assent will be though the VA Puget Sound. Enrolled participants will be referred to the intervention team at Kaiser and UC Davis. Study activities at the intervention sites will collect NIH data and will be approved by the Kaiser and UC Davis IRBs.

Refer to the Multisite Supplement and Kaiser and UC Davis IRB approvals for further information regarding this relationship. Henceforth this document will refer to the research activities and protocol conducted at the VA Puget Sound unless stated otherwise.

Principal Investigator: *Kristina Crothers, MD.* Along with the other MPIs, Dr. Crothers will oversee and be responsible for all administrative and scientific aspects of project development, implementation of all policies, procedures and processes, monitoring for quality and participant

safety, analyses, manuscript preparation, and dissemination of results. She will collaborate with VACS and work with the programmer at Puget Sound to identify potentially eligible participants, namely Veterans with HIV infection who currently smoke. She will work with the programmers to obtain VA electronic health record data, including comorbidities, laboratory and pharmacy data on participants. She will oversee the initial recruitment, enrollment, and randomization of participants, and the assessments of cotinine measures. She will work with the biostatisticians and the rest of the study team to analyze and interpret study data in years 4-5, and will plan activities for future dissemination working with key stakeholders within the VA. She will attend weekly all-site meetings with the other PIs, as well as conduct regular weekly meetings with the Coordinating Center team at Puget Sound.

VA Puget Sound staff

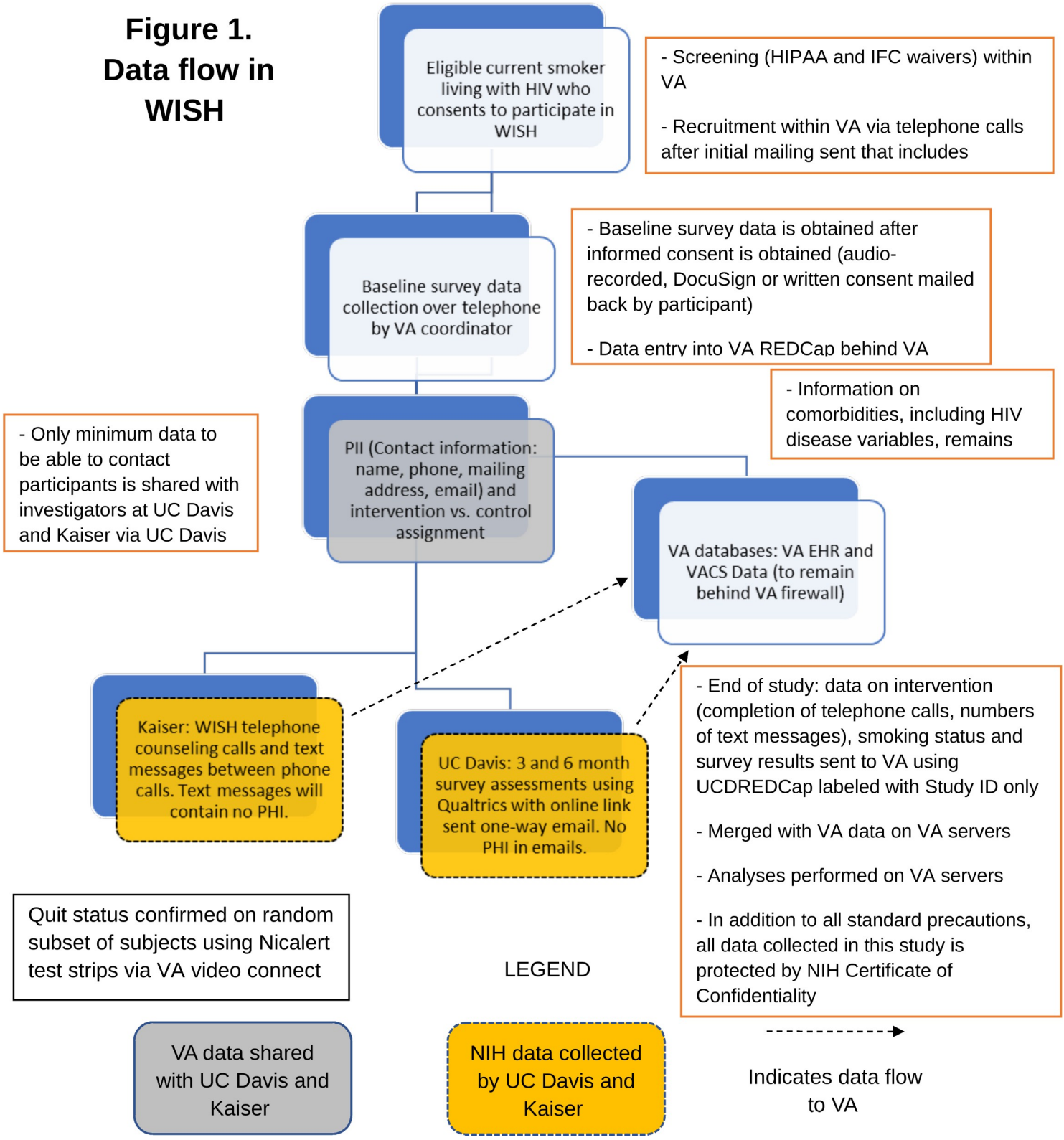
- The **Study Coordinator / Project Manager** will be responsible for overseeing and conducting patient recruitment, enrollment, and follow-up. She will complete data entry; conduct patient assessments of smoking status; maintain IRB compliance; and maintain databases.
- The **Programmer** will extract data to identify potentially eligible participant through the corporate data warehouse (CDW) and to retrieve baseline current data on comorbidities, medications, laboratory and other electronic health record data on participants. The Programmer will develop and maintain data collection and participant tracking databases. She/He will work closely with other team members to assemble data into analytic files.
- The **Analyst** / **Biostatistician** will be responsible for helping to create a study design and analysis plan that follows sound statistical principles. He will conduct statistical analyses, prepare interim and final reports, and assist with interpretation of data.

5.0 Study Procedures

5.1 Study Design

SEE DIAGRAM BELOW FOR DATA FLOW.

Figure 1. Data flow in WISH



STUDY & INTERVENTION DESIGN

First, we will randomize 20 participants to an initial Vanguard pilot trial, which will allow us to test all study implementation procedures prior to exposure of participants in the main trial, including VA video connect to test for feasibility for the cotinine dipstick quit verification later used on a random subset of subjects who report quit status at the end of the study. Study participants will complete a cotinine test within 3 weeks of completing all study activities and after being randomized. This will be conducted by study staff members at the VA. If staff are unable to reach participants within this time frame, they will not be eligible to complete the cotinine test. These participants will be observed for up to 12 months after intervention, and this data may be included in the final data analysis.

Then, eligible smokers who are living with HIV (n = 226) will be randomized to one of two treatment conditions: standard care control or the experimental intervention (aka, WISH) using a parallel, two-arm, randomized controlled trial and followed for one year to assess change in smoking behavior and other secondary outcomes. VA-based research activities will include recruitment, consent, randomization, data collection from VA electronic health records, and data analysis. Behavioral intervention activities and behavior change evaluation across both study arms will be conducted by non-VA sites. The data collected will be NIH data. After the intervention, data will be sent to the VA for analyses.

Standard Care Control: Control participants will be advised to quit smoking and referred to standard care treatment services provided nationally by the VHA. This includes access to a multi-call, tobacco cessation quitline program (1-855-QUIT-VET), encouragement to sign up for SmokefreeVet, an automated texting program to support cessation efforts, and access to FDA-approved pharmacotherapy for smoking cessation, provided through their local VA medical center pharmacy. Participants will be strongly encouraged to request a standard course of FDA-approved pharmacotherapy such as NRT (patch, gum, or lozenge), which is the first line smoking cessation medication within the VA, or other medication as deemed individually appropriate by their VA provider.

Experimental Intervention: Experimental participants will be offered a proactively-delivered phone-based counseling program with integrated intersession text message support delivered by the research staff at KPWHRI. Messages will be sent using an application called StudyPages , that is IRB approved through KPWHRI. We cannot guarantee the security of electronic communications**)**..Texts will not include sensitive health information but will be reminders about appointments and general messages to check in on your progress with your goals. Participants will also be encouraged to request a standard course of FDA-approved pharmacotherapy such as first-line NRT or other medication as deemed individually appropriate by their VA provider. Phone sessions will be recorded to ensure that the counselors are covering all topics that need to be covered in the sessions. Participant name will not be included in the recordings. Participants may refuse to have their sessions recorded. All recordings will be stored on a secure server at Kaiser Permanente and will be destroyed after data is analyzed for the study. Destruction/sanitation of research data after the project completion will be in accordance with the RCS 10-1 and Directive 6500. KPWA is a HIPAA covered entity and complies with all HIPAA regulations regarding data security. We will apply the same standard of protections to our study records. More specifically: All study files will be maintained in a centralized location on the KPWHRI departmental server. Access to this data is password protected and subject to the same security protections as other confidential health plan data. Access will be limited to staff working on this study and require access to these files. All staff are trained in appropriate

security protections, computer passwords are changed on a regular basis, and all staff sign annual confidentiality agreements.

Nicalert Quit Status Confirmation: A random subset of participants reporting they have quit using nicotine products at the end of participation will receive a Nicalert test kit to complete to confirm quit status. This is a saliva test that can be completed at home. Participants will be guided through taking the test via VA video connect, a secure technological platform behind the VA firewall used by VA providers for remote consultations with patients and recently approved for research use. Pioneering this technology with a research population will contribute to innovative use of technology in research settings. See the link to VA video connect privacy here: https://mobile.va.gov/app/va-video-connect#AppFAQ. A screen shot using the snipping tool will be taken of the test strip only and stored on a secure server at the VA. The participant will not be in this screen shot. After test completion, study participants will throw the test kit and strip away.

How risks will be minimized

This study is designed to specifically minimize risks to subjects.

IRB Oversight. All research activities will be reviewed and approved by the IRB at each site involved in human subjects' activities: VA Puget Sound, Kaiser Permanente Washington Health Research Institute (KPWHRI), University of California, Davis (UCD), and the West Haven VA. Each IRB will ensure participants are adequately protected against risk and all research activities are HIPAA compliant.

Informed Consent. As the VA has done in prior intervention trials, we will obtain a waiver of informed consent and HIPAA Authorization from the Puget Sound VA IRB to collect and use information necessary to identify potential participants for initial study contact.

Contacted Veterans will provide verbal consent to be screened for eligibility and to participate in the study. Consent to participate will include permission to collect required study information from participants' VA and VACS records; to share the minimum necessary study relevant information among study sites/investigators; and to contact participants for the purposes of this study. Paper and electronic communications will not include reference to HIV status or sensitive health information (PHI). While we will verbally tell participants that the study is designed for smokers who are infected with HIV, the written information statements and other study materials will not refer to HIV but will only refer to "certain chronic health conditions." Patients will have the option to get reminder text messages about their upcoming appointment to complete their baseline surveys or their cotinine test. These text messages will be issued from a VA phone and will not contain any sensitive information.

Participants will be fully informed of the potential risks of participation, alternate treatment options, and their right to discontinue study participation at any time. Participants will also be free to refuse to answer any survey questions.

Internet. **Any activity on the internet involves risk and, in using your own computer, you should take the normal precautions of ensuring that your system is running the most current version of your browsing software, that you have up-to-date virus protection, and that you implement a software or hardware firewall to protect your computer and yourself. If you choose to use a public computer to access this resource (such as a library computer), know that your information is only as safe as that computer's safety features.**

Any website can be hacked. By ensuring your computer has up-to-date security measures, you can reduce the risk to yourself, but risk cannot be totally eliminated.

Breach of confidentiality. We will implement and strictly adhere to multiple measures designed to protect participant confidentiality and ensure data security. Each level of data security is described below in Section 7.0 Privacy and Confidentiality. As a result of these measures, we do not expect any invasion of privacy or breach of confidentiality for any patient included in this project.

Potential Benefit of Research to the Subject and Others
Participants may benefit from this study. All participants may receive some satisfaction or indirect benefit from contributing to this research designed to encourage people living with HIV to quit smoking. Additional benefits include assistance quitting smoking. Participants in the WISH intervention may also benefit from other positive health behavior changes instigated by participation in this wellness intervention. Participants who stop smoking may experience reduced disease risk and potentially better management of existing chronic conditions, including HIV infection.

Society may benefit from this study. Study results will provide critical information about the comparative effectiveness of a wellness-based smoking cessation intervention designed for SLWH versus referral to standard care services available to Veterans. If the intervention is found to be effective, it could be disseminated nationwide through the National VA Quitline, thereby reducing smoking prevalence and improving health outcomes among the largest patient population of smokers living with HIV in the country. If effective, WISH could also be rolled out to other Veterans through the National VA Quitline, helping to expand the reach and effectiveness of cessation interventions offered to all Veterans in this country. The study will leverage existing VA data resources to expand knowledge about how to reduce disparities in smoking rates, uptake of cessation services and associated clinical health outcomes for SLWH.

5.2 Recruitment Methods

Number of subjects: This study will enroll up to 520 participants.

PARTICIPANTS AND RECRUITMENT

Veterans who are HIV+ and are current smokers will be recruited by study staff at the VA Medical Center-Puget Sound from the 9 VA medical centers participating in the Veterans Aging Cohort Study (VACS). Participants will be identified from the VACS cohort and the broader sample of HIV+ patients treated at these 9 medical centers; about 2,000 smokers. As needed, recruitment will be expanded to include eligible patients from the larger national cohort of HIV+ Veterans treated in the entire VHA system; about 8,000 smokers.

Potentially eligible Veterans will be identified using VACS data and medical records from the VA corporate data warehouse (CDW) and identify HIV+ current smokers who do not have documented exclusions (e.g., dementia, cognitive impairment). Next, they will be mailed a study postcard and sent an encrypted initial email notifying them of the future mailing of research study materials. This postcard and encrypted initial email would also have a study phone number if the veteran would be interested in gaining additional information. Emails will be encrypted using software Azure. In addition, the initial email will include that they can respond to the email to

notify staff they are interested in being contacted and will not contain any sensitive information such as PHI or PII. At least 7 days after this postcard mailing, potential participants will be mailed a study invitation letter (Attachment A Invitation Letter). The mailing will also include a study flyer describing the study (Attachment B Flyer) and the study information sheet (Attachment C Information Statement). Interested individuals will be screened by phone (Attachment D Recruitment Script). Eligible subjects will be called by the study team if we do not receive an opt-out card (included with study invitation letter) or receive an opt-out message on the study phone line. Previously contacted participants that were unable to be reached via 3 phone call attempts and have not responded by an opt-out post card will be sent a final follow-up email notifying them of the option to participate in the study

As another route for recruitment, advertising specialists with Trialfacts will post IRB approved advertisement materials to a given platform (Facebook for initial trial period). Interested veterans will be able to click on the advertisement that will prompt them to complete a brief Trialfacts screening questionnaire. This will include smoking status, HIV+ status and confirm that the patient is receiving care at a VA Medical Center. If eligible, Trialfacts will collect participant name and phone number and transfer this information via Azure RMS encryption on a password protected document to VA research staff. VAPS staff will then contact potential participant and confirm eligibility.

No sooner than 6 months following initial screening, research staff will re-contact previously interested ineligible veterans who reported smoking less than 5 cigarettes or were actively using NRT during initial screening. Veterans will have the option to opt out of recontact during initial screening going forward. Research staff will call these veterans up to three times to determine if veterans are still interested and now eligible. If they are still not eligible at time of re-contact, no additional recruitment attempts will be made.

If eligible, they will provide verbal consent, and the conversation will either be recorded as a means of documenting informed consent prior to randomization. Participants who cannot complete the baseline survey at the time of the initial call, and who do not follow-up to complete this survey will be called up to but not exceeding 3 additional times and mailed a letter (Attachment F Enrollment Letter) asking them to complete the survey if they do not respond.

Potentially eligible Veterans (HIV+ and are current smokers) who attend VAPS ID clinics may also receive a flyer about the study from clinic staff. Clinic staff will be notified via email from the study Principal Investigator (Dr. Crothers) about the study goals, copy of the study flyer, and location of additional printed copies of the flyer stored within the clinic. Providers will be instructed to distribute the flyer to any patients who are actively smoking and HIV+, and direct patients to contact the research team directly via the study phone line for screening and informed consent or communicate patient identifying information via MS TEAMS secure chat. Providers will not be recruited into the study nor facilitate in participant informed consent procedures.

Materials to be used: Study Invitation Letter, Study Recruitment Postcard, Flyer and Information Statement; Recruitment Script, Study Recruitment Email

Participant Compensation: If veterans call the VA study line to learn more about enrolling, they are eligible to receive a $20 incentive payment. This will be in the form of a gift card or direct

deposit and enrollment into the study is not a requirement. Veteran status must be verified by a study staff member in cohort data pull prior to payment.

$30 for each of 3 surveys (baseline, 3-, 6-months post-enrollment) and a $10 dollar bonus for completing all three. Participants selected to complete a cotinine test will receive an additional $20. Participants should expect to receive their check via mail approximately 8-12 weeks after their completion of each survey. The VA or UCD will issue payment for the baseline survey. All follow-up surveys are being completed by UCD, they will issue payment for the 3 and 6 month surveys.

5.3 Informed Consent Procedures

We are requesting a Waiver of Informed Consent and HIPAA Authorization from the Puget Sound VA IRB to collect and use information necessary to identify potential participants for recruitment.

We are requesting a Waiver of Documentation of Informed Consent for study participation. Interested Veterans will provide verbal consent to be screened for eligibility and to participate in the study. During the oral assent process, research staff will answer all questions about study participation and ensure that the participant understands the decision to enroll in the voluntary study. Participants may opt to send back an electronic signature via DocuSign or a paper copy of the signed consent if they do not wish to be recorded or use DocuSign and complete a baseline assessment (Attachment E Baseline Questionnaire) Participants are informed that they may elect not to participate in any study activities and that they may cease participation in the study at any time.

All study personnel will be current with required VA trainings and will remain in compliance with these trainings throughout the study period.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria:

- In care in the VA
- HIV+ serostatus
- Currently smoking ≥ 5 cigarettes daily
- Access to cell phone with text messaging capabilities
- English speaking

Exclusion criteria:

- Psychosis, dementia or significant cognitive impairment documented in the EHR
- Documented or observed hearing or comprehension difficulties that would preclude participation in study telephone calls
- Currently receiving cessation counseling or using an FDA approved treatment to quit smoking
- Institutionalized or imprisoned
- Pregnant

5.5 Study Evaluations

Screening. Potentially eligible individuals will be identified using the VACS and CDW automated records which Dr. Crothers has access to within the VA. Individuals will be selected for contact after initial screening for their HIV status, smoking status, and lack of excluded medical conditions (e.g., no psychosis, dementia or cognitive impairment).
Persons who do not opt out of further contact will be called in about a one to two weeks after the initial mailing is sent to determine interest and eligibility, by asking questions detailed in the Patient Recruitment Script (Attachment D Recruitment Script). Individuals who are determined to be eligible and provide consent will then be asked to complete a baseline survey (described below, Attachment E) via telephone.

Survey Assessments. Assessment items include standard, validated measures. The first assessment will be conducted prior to randomization (Attachment E Baseline Survey). Smoking level will be used to establish study eligibility and to block randomize participants in addition to other criteria. To describe both arms, we will also assess *demographics* (e.g., age, race/ethnicity, sex, gender identity, sexual orientation, education, employment, income, service-connected disability, current living situation), *tobacco and nicotine use history* (cigarettes per day, years smoked, use of other tobacco and nicotine products including e-cigarettes, history of quit attempts in past year assessed with CDC BRFSS items), *nicotine dependence* (assessed with the Fagerstrom Test of Nicotine Dependence[126]) and *cessation treatment history*.

Assessments after the intervention will be conducted by the UC Davis research staff at 3 months (end of treatment) and also 6 months post-randomization in both arms. We will assess 12-month outcomes through VA EHR data that will include documented smoking status, and immune markers and VACS index scores for Aim 4 analyses. This allows us to assess intermediate IMB model constructs and abstinence/ quit attempt outcomes at the end of scheduled treatment, at the primary follow-up of interest at 6 months, and to have long-term follow-up for smoking related, HIV-related and service-related outcomes over a year study period. Interviewers will be blinded to intervention assignment. Each will be intentionally brief to enhance response and participants will receive a $30 incentive for completion.

Cognitive-behavioral change process measures consistent with an IMB framework will be assessed as follows**:** *HIV-Specific Smoking Knowledge* will be assessed using items validated in a survey of SLWH conducted by the study team[58]. We will assess *Self-efficacy (*for quitting smoking, reducing smoking, and for specific behavioral skills such as managing cravings, and stimulus control) using 10 point Likert scales for each construct, and *Motivation for quitting* (assessed by rating on a 1-10 Likert scale recommended by OBSSR's Behavior Change Consortium). *Nicotine Withdrawal Symptom Management* will be assessed with the self-report Minnesota Smoking Withdrawal Scale, Revised[127,128], which reliably measures symptom increases associated with cessation of nicotine intake and symptom alleviation associated with nicotine replacement[129].

A brief *Substance Use* battery includes the AUDIT-C alcohol screening measure[130], DAST-10 screening measure for illicit drug use and marijuana use [131], and 2 injection drug use history items (ever in past and 3-month use)[132]. *Depression* will be assessed with the 8-item version of the PHQ-9[133,134] that excludes the suicide item.

At each *follow-up*, we will re-assess baseline measures subject to change (e.g., cessation-related Information, motivation and behavioral skills; depression; substance use) and the measures described below:

Smoking abstinence and quit attempts: To facilitate comparison of treatment effects with other

published trials, the primary outcome of 7-day PPA will be assessed at 6 month follow-up by self-report. As is appropriate for a motivational intervention trial that enrolls participants regardless of readiness to quit, the presence of any quit attempt by 6 months following randomization will also be a primary outcome[135]. This BRFSS item[136] reflects both abstinence (all abstainers will have made a serious quit attempt) and motivation to quit smoking (persons truly motivated to quit will make a serious quit attempt) and is more appropriate than abstinence for participants not interested in quitting prior to enrolling in the intervention. Secondary smoking-related outcomes will include measures of 7-day and 30-day PPA, each assessed as a self-report of no smoking – even a puff – during each timeframe[137]; number of cigarettes smoked per day; and floating prolonged abstinence (a proxy for sustained abstinence appropriate for evaluating a motivational intervention, in which the start point "floats" based on one's actual quit date rather than a pre-defined target quit date)[138] at 3 and 6 months, and the number and duration of quit attempts and presence of any quit attempt at all follow-ups. For subjects reporting quit status, a random sample of 20% of these subjects will receive a saliva test kit in the mail to verify quit status. The subject will meet with research staff via VA video connect, which is approved for research use, and will take the saliva test while a VA staff member watches to verify identity and correct test completion. During the time it takes for the test to show a result (15-30 minutes), staff will ask additional questions about nicotine exposure and qualitative questions about their experience being in the study. When the test shows a result, VA research staff will use the snipping tool available on VA computers to take a screen shot of the image of the test strip. The subject will be instructed to stay out of the video shot while the strip is held up so that the picture is only of the test strip. There are no identifying marks on the test strip, including no mention of nicotine, HIV status, personal information, or other identifiable markings. The screen shot will be saved on the secure server behind the VA firewall in a separate folder available only to approved staff. The picture will be saved with only the study ID listed and no other identifying information listed. Pictures will be deleted at the same time as other identifiable study data links.

Cessation medication use and adherence: We will monitor use of NRT and other FDA-approved cessation medications (i.e., varenicline, bupropion) using both *self-report* and *electronic VA pharmacy records* (e.g., medication used, number of refills, days of therapeutic coverage dispensed). We will take advantage of VA's robust pharmacy and claims data to confirm NRT or other pharmacy refills. While NRT is the first-line and most prevalent cessation medication used in the VA, by monitoring all cessation medications, we will be able to understand if participants used/ switched to a different cessation medication during the study period vs. not using/ discontinuing treatment altogether. This will also allow us to describe the total days used of any cessation medication as an aggregate measure of adherence in addition to NRT total days. We will first assess total number of days each medication was used during the study period by relying on pharmacy records and adjust based on self-report as appropriate[139]. For example, if one received a 60-day supply of medication but reported only taking it 40 days, we will code as 40 days use; if one reports 60 days of use but only received 30-days, we will code this as 30 days use.

Other usual care treatment utilization: Utilization of behavioral treatments explicitly and not explicitly recommended or referred through the study will be assessed by self-report and automated records to characterize use of usual care cessation services.

Additional data will be collected from VACS, including most recent *CD4 count, VACS Index 2.0 of mortality risk* (based on weighted and combined routine clinical measures)[140-142], most recent *HIV RNA level*, current *antiretroviral medication prescribed, and antiretroviral adherence* (therapeutic coverage past 6 months) will be assessed at baseline and 6 and 12 months. We also use the VACS database to describe *HIV-related co-infections (e.g., HPV; Hep B & C);* and relevant *comorbidities* (e.g., COPD; non-AIDS defining cancers including lung, anal, Hodgkin lymphoma) at baseline and during the year study period.

The research team at VAPS will also complete a review of CDW/JLV in order to confirm if patients expired in the study and it was not previously captured by the existing methodology relying on patient self-reporting of AE/SAEs.

5.6 Data Analysis

Original Sample Size and Power.

This study was originally powered on the primary outcome of 7-day point prevalence abstinence at 6 months, assuming a base rate of 0.10 in the control arm. Based on this assumption, we proposed recruiting 250 people per arm for a total sample size of 500 individuals. This sample size would give us 80% power to detect an absolute difference of 0.07 in the PPA rates between arms with no attrition, and an absolute difference of 0.10 in the PPA rates with 20% attrition in each arm. For the binary secondary outcome of any quit attempt during 6 month followup, we assumed a base quit attempt rate of 20% to 25% in the control arm, which would give us 80% power to detect quit attempt rates of 12% and 13% in the intervention arm, respectively.

We computed effects detectable for this sample size assuming a two-sided, .05 significance test and used the normal approximation to the chi-square without continuity correction[144]. The exact difference between control and intervention groups which is detectable with 80% power depends on the rate of smoking cessation in the control group. Based on rates obtained in prior research with HIV+ smokers and uptake rates of smokers referred to standard cessation counseling services, we expect that the rate in the control group for 7-day PPA will be 10%[51,124,145,146]. In prior research with SLWH, Lloyd-Richardson and colleagues [51] found 10% of SLWH were abstinent at 6 months after receiving either self-help + NRT or a motivationally enhanced counseling program + NRT. Humfleet et al.[38] reported 7-day PPA rates of 15% at 6 months among SLWH provided brief counseling + NRT and 27% among participants receiving a computer-based program modelled on the standard self-help provided to controls + NRT. This suggests intervention can be effective among SWLH, increasing abstinence rates by more than 10% and that standard cessation may result in ~10% abstinent at 6 months. We used this to establish our expected abstinence base rate. This rate also reflects the fact that many controls will opt not to receive the cessation services available. We would have 80% power to detect a 10.0% intervention effect (confirmed 7-day PPA: 10% control vs. 20% intervention, OR=2.25).

Revised Power Analysis

In consultation with the DSMB, it was decided to use available data from the control arm at baseline and 6 months to inform a revised power analysis based on the most recent enrollment projections. Based on those projections, we expect to recruit a total of 113 people per arm for a total sample size of 226. Data from the intervention arm were not used in this revised power analysis to avoid interim assessment of intervention effects.

Summary of interim follow-up data in control arm

We had baseline data on 50 individuals in the control arm, 26 of whom had follow-up data at 6 months on quit attempts and 25 of whom had 6-month follow-up data on 7-day PPA. The observed 7-day point smoking abstinence rate among responders was 0.05 (1/25). Under the missing = smoker assumption, the 7-day abstinence rate would be 0.02 (1/50). The observed quit attempt rate was 0.54 (14/26). The average number of cigarettes smoked per day was 12.4 with a standard deviation of 9.8, compared to an average of 15.9 cigarettes smoked per day at baseline with a standard deviation of 9.1.

Revised Power Analysis

Primary Outcome - 7-day point smoking abstinence at 6 months

In the full sample where missing data are imputed under the missing = smoker assumption, we estimate having 80% power to detect an intervention effect that results in an abstinence rate of 0.16 in the treatment arm if the control arm abstinence rate is 0.05, and 80% power to detect an intervention effect that results in an abstinence rate of 0.11in the treatment arm if the control arm abstinence rate is 0.02. In the responder-only sample assuming a retention rate of 60%, we estimate having 80% power to detect an intervention effect that results in an abstinence rate of 0.21 in the treatment arm if the control arm abstinence rate is 0.05, and 80% power to detect an intervention effect that results in an abstinence rate of 0.15 in the treatment arm if the control arm abstinence rate is 0.02.

Secondary Outcome - Quit Attempt within 6 months

Assuming a quit attempt rate of 0.54 in the control arm and a retention rate of 0.60, we estimate having 80% power to detect an intervention effect that results in a quit attempt rate of 0.31.

Secondary Outcome - Cigarettes Smoked per Day

Assuming a standard deviation of 9 cigarettes smoked per day and a retention rate of 0.60, we estimate having 80% power to detect an absolute difference in the mean number of cigarettes smoked per day of 4.36 cigarettes. Assuming that the mean number of cigarettes smoked per day in the control arm is 12, this translates to an average of 7.64 cigarettes smoked per day in the intervention arm.

Summary Tables

Table 1: Intervention Effects Detectable with 80% Power

No. Enrolled	Retention Rate	Cessation Rate (Control Arm)	Cessation Rate (Intervention Arm)	Risk Difference
200	0.6	0.02	0.17	0.15
200	0.7	0.02	0.15	0.13
200	0.8	0.02	0.14	0.12
200	1.0	0.02	0.12	0.10
200	0.6	0.05	0.22	0.17
200	0.7	0.05	0.21	0.16
200	0.8	0.05	0.19	0.14
200	1.0	0.05	0.17	0.12
200	0.6	0.10	0.30	0.20
200	0.7	0.10	0.29	0.19
200	0.8	0.10	0.27	0.17
200	1.0	0.10	0.25	0.15
226	0.6	0.02	0.15	0.13
226	0.7	0.02	0.14	0.12
226	0.8	0.02	0.13	0.11
226	1.0	0.02	0.11	0.09
226	0.6	0.05	0.21	0.16
226	0.7	0.05	0.19	0.14
226	0.8	0.05	0.18	0.13
226	1.0	0.05	0.16	0.11
226	0.6	0.10	0.29	0.19
226	0.7	0.10	0.27	0.17
226	0.8	0.10	0.26	0.16
226	1.0	0.10	0.24	0.14
250	0.6	0.02	0.14	0.12
250	0.7	0.02	0.13	0.11
250	0.8	0.02	0.12	0.10
250	1.0	0.02	0.11	0.09
250	0.6	0.05	0.20	0.15
250	0.7	0.05	0.19	0.14
250	0.8	0.05	0.17	0.12
250	1.0	0.05	0.16	0.11

No. Enrolled	Retention Rate	Cessation Rate (Control Arm)	Cessation Rate (Intervention Arm)	Risk Difference
250	0.6	0.10	0.28	0.18
250	0.7	0.10	0.26	0.16
250	0.8	0.10	0.25	0.15
250	1.0	0.10	0.23	0.13

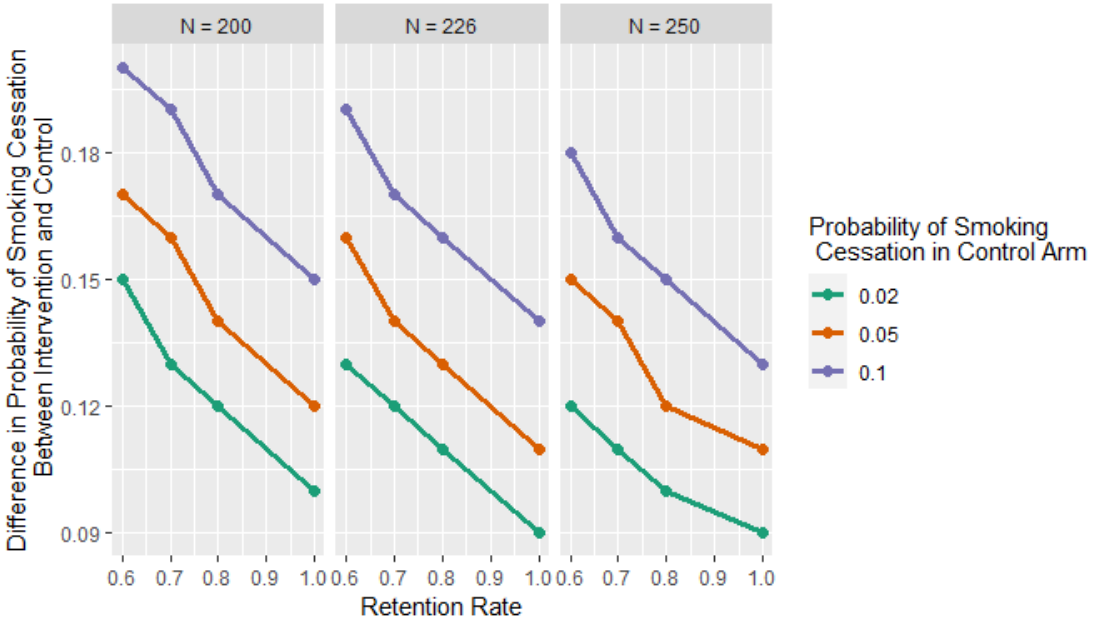


Figure 2. The effect sizes detectable with 80% power, expressed in terms of the difference in probability of smoking cessation between intervention and control arm, plotted against retention rates for different values of total enrollment (panels) and smoking cessation rates in the control arm (colored lines).

Data Analyses. All analyses will use an intent-to-treat (ITT) approach. Individuals will be analyzed by randomization group regardless of their utilization of assigned treatments. All analyses will be performed using the R statistical computing environment (https://www.R-project.org/). Robust sandwich-style standard errors will be used to account for potential violations of the model-based variance structures for linear and Poisson regressions. Confidence intervals for parameter estimates will be based on a confidence level of 95%. Hypothesis tests will be double-sided and based on a significance level of 0.05.

Aim 1. Compare the effectiveness of experimental and control arms by comparing 7-day PPA at 6 months, and patient reported 24-hour intentional quit attempts, prolonged abstinence, 7-day PPA, 30-day PAA, cigarettes smoked per day, at 3 and 6 months post-randomization.

Analyses of Primary Smoking-Related Outcomes. We will first use chi-square analyses to compare the percentages in the control and intervention groups who are abstinent by the confirmed 7-day PPA intent-to-treat measure. We will then repeat these analyses using logistic regression to control for the four baseline variables which we used in the block randomization (recruitment site, baseline intention to quit within 30 days, number of cigarettes smoked per day <10, sex), since failure to do so can result in biased estimates of the treatment odds ratio. In addition, we will fit a second adjusted model which adjusts for these stratification variables. In all of these analyses, anyone with missing data on smoking status at follow-up will be assumed to be smoking. Following the Russel Standard,[143] unless deceased, respondents who are missing PPA outcome data will be classified as smokers in the primary analysis. If missingness is non-differential between treatment arms, classifying non-responders as smokers will tend to produce a conservative effect estimate biased towards the null hypothesis of no difference between intervention groups. In the Dropout Analyses section, we describe alternative approaches we will use to examine the sensitivity of our estimates to this assumption.

For the outcome of 24-hour quit attempts post randomization, we will analyze this outcome both as a binary measure (none vs. 1+ attempts) and as a count type variable. For the binary measure, we will do unadjusted chi-square tests and adjusted analyses using the same two logistic models described above with the addition to the models of baseline number of quit attempts in the prior year. For the count version of this measure, we will compare mean number of quit attempts in the groups using t-tests/Wilcoxon tests (unadjusted analyses). For the adjusted analysis we will fit the same two models using either ordinary least-squares regression or Poisson regression (choice will depend on the shape of the distribution for the number of attempts). When smoking status is unknown or the quit attempt question is not answered, we will assume that the person made no quit attempts.

Analyses of Secondary Smoking-Related Outcomes. Analyses of number of cigarettes smoked per day, self-report PPA, and floating prolonged abstinence outcomes will be done in a similar manner to that used for the primary smoking outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). We will use regression modeling to examine the effect of the intervention over the entire course of follow-up, using generalized estimating equations (GEE) to account for the within-subject correlation over time. We will quantify a potential non-constant intervention effect over time using interaction terms. If there is sufficient evidence of a non-constant intervention effect, we will use month 6 follow-up as the primary time point of interest. Otherwise we will use the GEE regression model to estimate the effect of intervention using the entirety of the follow-up data.

Aim 2. Describe the reach and implementation of the HIV-specific comprehensive intervention.

Descriptive and bivariate analyses will be used to characterize absolute number, proportion and representativeness (in terms of current readiness to quit, smoking history and demographic characteristics, antiretroviral use, comorbidities such as non-AIDS defining cancers, and HIV-related co-infections) of smokers living with HIV who are willing versus unwilling to enroll in the program, who do or do not enroll in standard VA cessation services, and who use or do not use NRT or other cessation medications during the study period. Group comparisons will be made

using t-tests or Wilcoxon-Mann-Whitney non-parametric tests for continuous/ ordinal variables and chi-square for binary outcomes. In addition, we will use multiple regression models to explore how predictive these factors are in combination of willingness to enroll, utilization of VA standard cessation services, and use of cessation medications.

Aim 3. Compare cognitive-behavioral change process variables based on the Information-Motivation-Behavioral Skills Model for Smoking Cessation (i.e., HIV specific smoking-related knowledge, self-efficacy for quitting or reducing smoking, motivation to quit, and cessation-related behavioral skills including cessation medication use/ adherence) between the experimental and control arms at 3 and 6 month follow-up.

Analyses of intermediate change process outcomes will be done in a similar manner to that used for the smoking -related outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). For outcomes such as self-efficacy, adjusted models will always include the baseline measure of the outcome under analysis (note, we cannot do this for cessation since 100% are smoking at baseline). We expect to use least squares regression to analyze HIV-specific smoking knowledge, motivation to quit, self-efficacy for quitting and reducing smoking, and cessation-related behavioral skills, (possibly after a transformation to account for possible left or right skewness). We will use a similar approach to evaluate NRT and/or other cessation medication use and adherence. We will also test if the effect of the intervention is constant across the three follow-ups using GEE.

Aim 4. Compare CD4 T-cell count and VACS Index of mortality risk between arms at 6 and 12 months.

Analyses of secondary HIV-related outcomes will be done in a similar manner to that used for the primary and other secondary outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). For outcomes such as CD4 count and VACS Index, adjusted models will always include the baseline measure of the outcome under analysis.

The VACS Index is a validated, generalizable risk index for predicting all-cause mortality that uses routine clinical laboratory data[142,147]. We will compute the VACS Index 2.0 version based on the following variables obtained from the VACS database that are also in the original 1.0 version: age, CD4, HIV-1 RNA, hemoglobin, alanine and aspartate transaminases, platelets, creatinine and hepatitis C virus serostatus, along with the new variables of albumin, white blood count, and body mass index in the 2.0 version that improve discrimination for mortality[113]. Each 5-point increase in VACS Index 2.0 score reflects an approximate 1.3-fold increase in mortality, and preliminary analysis suggests scores are higher among current smokers compared to former or never smokers[113]. We will test the hypothesis that participants randomized to the intervention arm will experience a greater reduction in VACS Index 2.0 scores over 6-12 months compared to the control arm, potentially due to smoking reduction, smoking cessation and/or other wellness focused changes in behavior that may be reflected in the biomarkers of the Index.

Dropout Analyses. The Russel Standard of counting non-responders as continued smokers is appealing as a way to ensure uniformity in the handling of missing data in smoking cessation studies. However, it is difficult to justify statistically, and its impact on the scientific conclusions of a study must be considered. To this end, we propose to perform a thorough investigation of the impact of the “missing = smoker” assumption by considering several different statistical approaches to handling non-response. Estimates of the effect of the intervention under these

alternative specifications of the missing data mechanism will be compared to the estimates obtained using the “missing = smoker” assumption to see how sensitive our results are to this assumption.

The “missing = smoker” assumption is a form of deterministic imputation that can affect p-values and confidence intervals by artificially reducing the variance of the data[148]. To address this shortcoming, we will repeat the analyses of our primary outcomes using less deterministic imputation procedures. We will examine patterns of missingness in the two intervention arms to determine to what degree non-response differs between the two arms and to determine relevant baseline characteristics that are related to non-response. We expect variables such as readiness to quit and level of nicotine dependence to be important factors in these models, but other baseline variables may be included as well. We will then use these baseline measures to construct imputation models for the missing responses. Multiple imputation procedures will be used to correctly account for the uncertainty in imputed values, resulting in valid p-values and confidence intervals. First, we will refit the regression models described in the previous aims using the imputed data to obtain estimates of the effect of the intervention consistent with a Missing at Random non-response model. Then, we will conduct sensitivity analyses under the assumption of non-ignorable non-response, also referred to as Missing Not at Random[149]. As noted in Hedeker[148], the Russel Standard of counting all non-responders as continued smokers is itself a form of non-ignorable non-response, in that it assumes a direct relationship between missing status and the unobserved outcome. Since assumptions regarding non-ignorable non-response cannot be checked using the observed data, it is important to consider alternative specifications for these types of models. To achieve this, we will use a 2-step GEE imputation method[149]. This method provides a flexible and transparent approach to handling non-ignorable missingness that improves upon the Russel Standard both by accounting for the uncertainty of the imputation method when calculating standard errors as well as by incorporating available covariate information.

5.7 Withdrawal of Subjects

Participants may withdraw voluntarily from the study at any time. The participant will be disenrolled and will not participate in any further study activities. Dr. Crothers and the study sponsor may still use information that was collected prior to the subject’s withdrawal, unless the participant submits a written request to have their data withdrawn.

When subjects indicate that they want to stop the study during asynchronous communication (by leaving a message), we will seek clarification to understand what level of withdrawal from WISH they desire. We will clarify if they mean withdrawing from the study completely (from the intervention, surveys, and follow up data collection), breaks/stoppage of the study intervention, withdraw from surveys or follow-up data collection only. In the event that KP or UCD staff are unable to ascertain the level of desired continued involvement from participants, VA staff will call up to three times to achieve clarity or send a letter to participants. In the event that study staff are unable to re-connect with participants providing incomplete information, we will assume full withdrawal from the study.

6.0 Reporting

6.1 Data and Safety Monitoring Plan

Data and Safety Monitoring Board (DSMB). An independent DSMB will be established in accordance with VHA Handbooks 1200.05 and 1204.01, NCI policy, and in consultation with the VA Puget Sound IRB. The DSMB is convened to monitor data and safety for the clinical study and provide recommendations. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The DSMB is an independent group responsible for monitoring participant safety and data quality and evaluating the progress of the study. The DSMB will meet via teleconference once a year.

Safety monitoring.

If a serious adverse event (SAE) occurs, the PI will follow the policy and procedures established by the IRB. Specifically, the PI will report all SAEs to the IRB and local Research and Development (R&D) Office within five working days. SAEs will be reported even if the PI believes that the adverse events are unrelated to the protocol. In the event a study participant reports a SAE to a research team member, the team member will contact the PI. Problems/adverse events that are not serious that are related to the protocol will be reported to the IRB within 10 working days. All SAEs and problems (anticipated/expected or not) will be kept in a log.

While research staff will do their best to adhere to IRB approved research protocols, in the event that a protocol deviation is noted, action will be taken to rectify the protocol deviation. If research staff becomes aware of a protocol deviation, violation or noncompliance, the event will be reported to the IRB and all necessary reporting agencies within acceptable reporting requirements. Non-serious deviations will be reported on the next CRQ

DSMB Recommendations.

The DSMB can recommend that the current study continue without modification, continue with specified modifications, discontinue one or more arms of the study, or halt or modify the study until more information is available.

Recommendations of the Board are to be included in the materials for the subsequent DSMB meeting.

If the DSMB recommends a change for participant safety or efficacy reasons, or that the study be closed early, the MPIs should implement the change as expeditiously as possible. In the unlikely situation that the MPIs do not concur with the DSMB, then the NCI Division Director must be informed of the reason for disagreement. The MPIs, DSMB Chair, and NCI Division Director will be responsible for reaching a mutually acceptable decision about the study.

If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision. In the absence of disagreement, policies of the NCI Division that made the award under which the trial is supported should be followed in regard to amending the protocol or changing the award.

7.0 Privacy and Confidentiality

PHI will be obtained during the course of the study.

Breach of confidentiality. Multiple steps will be taken to protect participant confidentiality. Each level of data security is described below.

1. *Data storage*. VA, UCD, and KPWHRI are all HIPAA covered entities and will comply with all HIPAA regulations regarding data security. A data use agreement through the VA will be obtained to allow sharing of limited data with UCD and KPWHRI. All study files at each site will contain the minimum data necessary to accomplish the research activities at each site. Paper copies of records will be stored in locked files at the study team's work area at VA Puget Sound and will be accessible only to IRB-approved research staff. Electronic data access will be password protected and subject to the same security protections as other confidential patient data. Access will be limited to staff working on this study who require access to these files. Access to study data will be removed for study personnel when they are no longer part of the research team. All staff will be trained in appropriate security protections, computer passwords will be changed on a regular basis, and all staff will sign annual confidentiality agreements. Baseline surveys conducted at the VA will be done on the telephone, with data entry by the coordinator into VA RedCap database hosted on the VA server. Data necessary to contact individuals who consent to be in the study will be shared with UCD and KPWHRI investigators by entering data into UCD RedCap. Online surveys administered by UCD during the course of the intervention at 3 and 6 months of follow-up will be hosted also using UCD Redcap

2. *Data transfer*. Transfer of data between VA Puget Sound, UC Davis, and KPWHRI will take place using UCD REDCap, a web application tailored for multisite research studies to build and manage online project management databases. The REDCap program in general has sophisticated customizable capabilities important for quality and security including flexible form creation, granular user privileging, password management, user authentication, auto logout, logging and audit trails, data export and de-identification, and protective security measures. Only a limited dataset will be transferred from VA to KPWHRI or UC Davis, based on the terms of the DUA, containing the minimum required information necessary to contact the participants for the purposes of carrying out the intervention or coordinating follow-up surveys (this will include name, email, telephone number, and address as well as a variable to designate study assignment – intervention vs. control).

3. *Communication with participants*. Electronic communications from the intervention team at KPWHRI with participants may contain references to smoking behavior change goals set by participants (e.g., a reminder to practice not smoking in your car for a day) but will not contain sensitive personal health information (e.g., HIV serostatus, medication information).

4. *Participant identities.* Participants' identities will not be shared with anyone other than relevant study staff who need this information to perform their study roles. Identifiable information will not be kept with other study data. Participants will be identified only by study ID number that will be sequentially generated and will not contain any HIPAA identifiers in part or in entirety. The crosswalk that links the study ID number to the identifier will be stored in on the secure VA Puget Sound HSR&D drive (i.e. J drive) in a

restricted-access, project-specific folder, to which only IRB-approved research personnel will have access.

5. *Reporting.* To report study results, we will use only aggregated data or otherwise unidentifiable data.

8.0 Communication Plan

VA Puget Sound researchers will hold regular phone and/or Skype meetings with the intervention teams at UCD and KPWHRI. These meetings may include co-investigators from the West Haven VA and FHCRC. During these meetings, any changes to protocol, informed consent, HIPAA authorization, or initial and continuing IRB approvals will be announced. The intervention team will be alerted via during the teleconference of any serious adverse events or unanticipated problems. Issues requiring more urgent attention will be communicated promptly upon learning of them via email and phone with the entire study team. All current documents will be made available to the intervention teams via email.

9.0 Information Security and Data Storage/Movement

The Puget Sound VA staff will first enter data coded with a confidential Participant ID into a VA REDCap database, hosted by the VA behind the VA firewall. VA REDCap is a free web application tailored for research studies to build and manage online surveys and databases. VA REDCap has sophisticated customizable capabilities important for quality and security including flexible form creation, granular user privileging, password management, user authentication, auto logout, logging and audit trails, data export and de-identification, and protective security measures. Data collection during the screening phone calls will be first captured on paper forms and then entered into VA REDCap by a study coordinator. This data will include the results of the screening phone call and the baseline survey for participants who consent to enroll.

Based on the terms of the DUA, staff at the VA Puget Sound will then enter the minimum contact information into a different UCD REDCap database. Data entered by staff at the VA Puget Sound into this database will be limited to patient eligibility and minimum contact information necessary to contact the participants for the purposes of carrying out the intervention or coordinating follow-up surveys. The results of the baseline surveys will not be entered into this database.

Data entry by VA study staff will be done on VA computers to ensure its security. Users access VA REDCap via a user specific login and password. Access to the VA REDCap WISH project will be restricted to individuals who have demonstrated proficiency with the data system. The study staff at VA Puget sound will closely monitor: a) participant accrual in relation to goals and timeline; b) the randomization

process and group comparability on the balancing variables; c) key baseline characteristics of the sample, by group.

At the end of the intervention, NIH data collected by KPWHRI and UCD as approved by their IRBs will be sent to the VA Puget Sound for analyses. All data will be transferred within the guidelines of the terms outlined by the existing DUA. Data will be merged with VA data, cleaned and verified, then downloaded into appropriate analysis software housed by the PLG on the VA Center of Innovation for Veteran-Centered and Value-Driven Care (COIN) secure computer network servers and handled in accordance with the COIN's extensive data security policy. The study data is backed up daily and maintained by the COIN. One official copy of all study data and a master data dictionary will be maintained and updated regularly by the study data manager. A specific folder will be created by COIN IT staff located on the J Drive for storage of electronic data.

All study information is accessible only by IRB approved study staff on a need-to-know basis. Limited analytic datasets are shared between authorized study personnel via secure transmission and/or via a secure virtual private network employing industry-standard password protection and data encryption. Study information is not disclosed to any third party except as required by law. Only aggregate data will be used to report study results. Patient identifiers will be retained per IRB permissions.

The data will be retained on the VA Puget Sound Health Care System network server or OI&T managed archived back-up media. If a new RCS is published prior to the end of this study all files with identifiable data for this study will be deleted from the VA Puget Sound Health Care System (VAPSHCS) network server folder no later than six months prior to the closure of the study. Once identifiable data can be destroyed, only deidentified data will be retained thereafter on the VAPSHCS network server. Otherwise, all data will be retained until the RCS is published.

Deleted files are recoverable only by Office of Information and Technology (OI&T) network administrators from back-up tapes maintained by VAPSHCS OI&T. The VAPSHCS HSR&D network backup and retention policy limits retention of network backup tapes containing protected health information to no more than six months from the date that the data were deleted from the network server. After six months, monthly backup tapes are reused for disaster recovery or new monthly backup purposes. If the backup tape fails or is no longer in use for any reason, it will be destroyed by VAPSHCS OI&T staff, in compliance with VA policies for destruction of this
media type. Therefore, the identifiable data for this study will not be recoverable, consistent with IRB requirements.

10.0 References

Bibliography of cited literature

Appendix: WISH Supplement Study Protocol

Improving the Reach and Effectiveness of Smoking Cessation Services Targeted to Veterans Living with HIV

[MIRB # 01818]

Funding Agency: National Cancer Institute

Principal Investigator: Kristina Crothers, MD

April 2021

Abstract

Tobacco use remains the leading preventable cause of death and illness in our society, and smoking rates are disproportionately high among people living with HIV. Research suggests SLWH are largely unaware of the HIV-specific deleterious effects of smoking and often lack motivation and confidence in their ability to quit. For these reasons, we developed the Wellness Intervention for Smokers with HIV (WISH). WISH is grounded in the Information-Motivation-Behavioral Skills (IMB) Model and delivered remotely by mobile phone (voice and text message). The program is designed for *all* SLWH, regardless of their initial motivation to quit. WISH follows evidence-based, best practice guidelines for nicotine dependence treatment, but is innovative in its use of a more comprehensive wellness approach. That is, the intervention addresses both smoking and a number of other personally relevant health behaviors (such as treatment adherence, stress/mood, nutrition, other substance use, etc.), making it relevant and engaging to all SLWH, not just those ready to stop smoking. For those not yet ready to quit, WISH is designed to build and strengthen motivation and self-efficacy for quitting, while smokers also work on other personal health goals. Once ready to quit smoking, participants receive evidence-based cognitive-behavioral counseling and encouragement to use nicotine replacement therapy (NRT) or other appropriate pharmacotherapy. WISH builds on our extensive experience creating motivationally-enhanced cessation interventions and has been pilot tested with SLWH. In this trial, we will compare the effectiveness of WISH to standard care services offered through the National VA Quitline and the SmokefreeVET texting program, NCI-supported tobacco cessation services available to all Veterans. Participants in both arms can receive phone/ text counseling and have access to pharmacotherapy through VA. Primary outcomes will be 7-day point prevalence smoking abstinence and presence of any 24-hour intentional quit attempts. Secondary outcomes will include prolonged abstinence, change in cigarettes per day, intermediate change process outcomes based on the IMB model, as well as metrics of intervention reach and implementation. We will also describe comorbidities and explore intervention impact on markers of immune status and mortality risk using the outstanding clinical data resources available through the Veterans Aging Cohort Study (VACS). If effective, WISH could meaningfully reduce smoking among HIV+ Veterans nationwide. To support this goal, dissemination efforts are planned in Year 5 to share the WISH program with the National VA Quitline. Because VA is the largest U.S. provider of HIV care, this research has the potential for significant public health impact. In an additional supplementary aim, we will qualitatively examine how alcohol and tobacco synergies that drive long-term cancer risk are impacted by HIV, social determinants and mental health conditions, which can inform more effective interventions for high-risk populations.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

- Acquired Immunodeficiency Syndrome (AIDS)
- Agency for Healthcare Research and Quality (AHRQ)
- American Thoracic Society (ATS)
- Antiretroviral therapy (ART)
- Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)
- Body mass index (BMI)
- Behavioral Risk Factor Surveillance System (BRFSS)
- Cardiovascular disease (CVD)
- Cardiovascular risk factors (CVRFs)
- Centers for Disease Control and Prevention (CDC)
- Centers for Medicare and Medicaid Services (CMS)
- Chronic obstructive Pulmonary Disease (COPD)
- Cluster of differentiation 4 (CD4)
- Drug Abuse Screening Test (DAST)
- Electronic health record (EHR)
- Food and Drug Administration (FDA)
- Generalized estimating equations (GEE)
- Health Insurance Portability and Accountability Act of 1996 (HIPAA)
- Human Immuno-deficiency Virus (HIV)
- Human papillomavirus (HPV)
- Information-Motivation-Behavioral Skills (IMB)
- Institutional Review Board (IRB)
- Kaiser Permanente Washington Health Research Institute (KPWHRI)
- National Institutes of Health (NIH)
- National Cancer Institute (NCI)
- Nicotine replacement therapy (NRT)
- Office of Behavioral and Social Sciences Research (OBSSR)
- Patient Health Questionnaire (PHQ)
- Point prevalence abstinence (PPA)
- Protected Health Information (PHI)
- Principal Investigator (PI)
- Randomized Controlled Trial (RCT)
- Research and Development (R&D)
- Research Electronic Data Capture (REDCap)
- Ribonucleic acid (RNA)
- Smokers Living with HIV (SLWH)
- Standard Care (SC)
- Transport Layer Security (TLS)
- University of California Davis (UCD)
- University of Washington (UW)
- United States Preventive Services Task Force (USPSTF)
- Veterans Affairs (VA)
- Veterans Aging Cohort Study (VACS)
- Wellness Intervention for Smokers with HIV (WISH)

Contents

Protocol Title:.....5
1.0 Study Personnel.....5
2.0 Introduction.....5
3.0 Objectives.....5
4.0 Resources and Personnel.....5
5.0 Study Procedures.....6
5.1 Study Design.....6
5.2 Recruitment Methods.....6
5.3 Informed Consent Procedures.....7
5.4 Inclusion/Exclusion Criteria.....7
5.5 Study Evaluations.....7
5.6 Data Analysis.....7
5.7 Withdrawal of Subjects.....7
6.0 Reporting.....8
7.0 Privacy and Confidentiality.....8
8.0 Communication Plan.....8
9.0 Information Security and Data Storage/Movement.....9
10.0 References..... .9

Protocol Title: Improving the Reach and Effectiveness of Smoking Cessation Services Targeted to Veterans Living with HIV

9.0 Study Personnel

Principal Investigator:
- Kristina A. Crothers, MD, 206-277-3013, Kristina.Crothers@va.gov

Co-Investigators:
- Emily C. Williams, PhD, MPH, (206) 277-6133, Emily.Williams3@va.gov

Collaborators (at other institutions, not covered under the VA IRB approval):
- Jennifer B. McClure, Jennifer.B.Mcclure@kp.org
- Sheryl L. Catz, scatz@ucdavis.edu
- Jaimee Heffner, jheffner@fredhutch.org
- Kathleen Akgün, Kathleen.akgun@va.gov

10.0 Introduction

SIGNIFICANCE AND SCIENTIFIC PREMISE.

PRIMARY INTERVENTION STUDY

Smoking is a leading preventable cause of death and illness[1], including among people living with HIV (PLWH). Smoking rates are exceptionally high among PLWH, often 2-3 times higher compared to the general population[2-14] and the deleterious effects of smoking are compounded among PLWH who smoke, contributing to health disparities. The most common non-HIV-related causes of death include the tobacco-related conditions of cardiovascular and pulmonary disease, non-HIV-related cancer (most of which are directly related to tobacco use), as well as liver disease, alcohol and other substance use and disorders[15-21]. In recognition of this shift, the Infectious Diseases Society of America recommended that health care for PLWH expand from a primary focus on HIV-related illnesses to include other preventable conditions[22]. We and others have shown that smoking is associated with reduced quality of life, increased risk of bacterial pneumonia and other AIDS defining illnesses, lung cancer and other malignancies, and two-fold greater mortality for PLWH who smoke compared to those who do not[3-5,14,20,23-28]. Smoking is also the most significant modifiable risk factor for many non-AIDS defining chronic conditions, including cardiovascular disease and chronic lung disease[17,18,28-32]. Notably, smokers may have poorer viral and immunologic responses to antiretroviral therapy (ART) and higher risk of developing AIDS[15,23,33,34] . *In sum, smoking cessation is critically important to improve health in PLWH.*

Calls for research and limited evidence base. In recognition of the health disparities caused by smoking among PLWH, NIH and others have called for more research to inform the effective treatment of smoking in this high-risk population[13,35-45]. *The proposed research is responsive to this call.* Amazingly, a 2014 systematic review found that only 5 published RCTs had tested cessation treatment among SLWH[46] and a 2016 literature synthesis characterized the cessation literature for SLWH as sparse and with mixed efficacy findings[47]. As a result, the empirical evidence base to inform how best to promote cessation in this high-risk population is limited. Standard care

smoking cessation services appear inadequate to address the needs of SLWH given that smoking rates remain so *exceptionally high* among SLWH compared the general population.[1,7,12,43] Moreover, the limited evidence to date does not support a standard-care approach with SLWH; a recent Cochrane review showed pooled long-term abstinence of standard care controls was 8% among 6 studies conducted with SLWH[48].

Review of prior studies: A case for a *new* type of evidence-based intervention strategy. Studies that have tested standard care (i.e., cessation counseling + pharmacotherapy) or some version of this among SLWH failed to find that traditional enhancements to this strategy were sufficiently effective[48]. For example, in a single arm longitudinal study where 247 SLWH were given an intensive best practice cessation intervention (12 weeks of cognitive behavioral telephone counseling + varenicline or nicotine replacement therapy [NRT]), cotinine-confirmed abstinence was only 10% at 12 months.[42] An intervention comparing standard care advice to quit + NRT to 8-session tailored group therapy among 145 SLWH did not find significant differences between the arms even at an immediate post assessment point of 3 months (9.2% versus 19.2%)[49] and an online cessation program compared to usual care advice also found low rates in both arms overall (10% vs. 4%) with abstinence reaching 18% only among those completing all 8 online sessions[50]. In one of the largest trials conducted with SLWH (n=444), participants were randomized to 2 brief sessions of in-person standard care + self-help + NRT or 4 sessions of in-person motivational interviewing + NRT. Smoking abstinence rates at 6 months were equivalent in each arm (9-10%), suggesting that cessation-focused in-person strategies were not an effective way to enhance motivation in SLWH[51], and that more innovative or comprehensive strategies are warranted. Importantly, the cessation rates in these studies are well below the long-term quit rates observed in non-HIV populations provided phone counseling + pharmacotherapy (abstinence range 24% - 32%)[35]. Some of the most promising studies with SLWH come from remotely-delivered interventions, improving reach[52]. For example, Gritz et al.[39] found urban SLWH offered cell phone counseling were 2.4 times more likely to quit than people receiving usual care (P = .049), and Humfleet et al.[38] reported 7 day PPA rates of 27% at 6 months among SLWH who received a computer-based intervention + NRT. Thus, there is good reason to believe that remotely delivered counseling interventions will be more effective than "standard care" interventions with SLWH, particularly if smokers remain engaged in the program, but overcoming barriers to access alone will not be sufficient to enhance cessation rates. *We contend that for interventions to be more effective with SLWH, they need to utilize more appealing or comprehensive strategies to overcome traditional barriers to care, and their content also needs to be adapted and tailored to meet the unique needs and interests of SLWH. Moreover, programs need to cast a broad net and not be limited to those ready to quit*, as explained below.

Enhancement to standard care #1: Intervene with smokers, regardless of readiness to quit. It is well documented that most smokers want to quit someday, but at any given time, only ~ 20% or less are ready to quit smoking in the next month[53-57]. This holds true among SLWH. We found that 21.5% of SLWH surveyed were in the Preparation stage (ready to quit smoking in the next month), whereas 68% were in the Contemplation stage (thinking about quitting in the next 6 months, but not next month)[58]. We call this latter group "ambivalent" smokers. Most "standard care" interventions are only designed for those smokers who are ready to take action to quit, not those who are ambivalent. *This is a significant treatment gap*, especially because research has shown that ambivalent smokers are interested in receiving intervention services and will reduce their smoking levels in response to intervention.[59] In our prior work, we found ambivalent smokers are willing to enroll in clinical trials when it is clear that the goal is to help them explore their willingness to quit or to answer questions about the quitting process, as opposed to asking for a commitment to stop smoking; many even successfully quit.[60,61] Others have shown that setting a goal of smoking reduction increases quit rates among ambivalent smokers, particularly

when counseling is paired with a stop-smoking medication[62-66]. *Thus, there is good reason to expect interventions targeting ambivalent smokers can be effective, particularly if they are designed to be sensitive to smokers' ambivalence*. Fagerstrom suggests ambivalent smokers require softer, more gradual intervention approaches, even if they contain some of the same basic behavioral and pharmacological strategies that are effective with smokers who are ready to quit.[67] This recommendation is consistent with West's PRIME theory of motivation, which suggests motivation and stage of change are highly fluid and change quickly over time.[68] As a result, West argues there is no reason to exclude ambivalent smokers from treatment; rather, we need to modify interventions to be more engaging to them, in addition to those ready to quit. *This is the goal of the proposed intervention*.

Intervening with smokers, regardless of their readiness to quit, is a paradigm shift that could be an important tactic for reducing smoking, particularly among vulnerable smokers such as Veterans and PLWH. This approach has been demonstrated to be effective among low socioeconomic status (SES) smokers at all levels of readiness to quit in both general population and Veteran-only samples. Work conducted by Fu et al., which specifically focused on proactive outreach to low SES smokers in both VA and non-VA settings, showed a 30-50% increase in the odds of quitting at 1-year post-intervention as well as 6 times higher odds of using evidence-based tobacco treatment[69]. Such findings support our general research premise that targeting smokers at VA, regardless of their readiness to quit, may be an effective way to improve the reach and effectiveness of cessation treatment among SLWH. However, for these interventions to be effective, they must be able to both motivate smokers to want to quit and support their cessation efforts. Effective motivational treatments are generally lacking in this population[70] and more research in this area has been called for[35]. In fact, almost all research among SLWH to date has focused on those ready to quit, or has used relatively brief interventions that yielded low 6-month abstinence rates among those not committed to quit (9-10%)[51], suggesting that more intense or comprehensive intervention may be needed in this population. *We hypothesize it is necessary to not only provide motivational counseling and medication access, but also cognitive-behavioral skills-based counseling, HIV-specific smoking cessation education, and relatively intensive contact to effectively intervene with SLWH. Additionally, to fully engage SLWH who are not ready to quit smoking, it may be important to integrate the counseling in a broader wellness-based intervention*.

Enhancement to standard care #2: Integrate smoking cessation into a comprehensive wellness-based approach tailored to PLWH. SLWH require interventions designed to meet their unique treatment needs[36,71]. Quitting in this population may be complicated by high rates of depression and other substance use[58,72], both of which are common in this community and known to make cessation more difficult[71,73,74]. Moreover, many people are unaware how HIV and tobacco use interact to put their health at risk, and some may have low motivation or lack the skills to add smoking reduction to their already extensive HIV self-care activities[, 6,58,75-77]. SLWH may perceive HIV as their only health concern and many perceive strong coping benefits to smoking, with few perceived risks[58,77-79]. Others perceive smoking cessation as another burden, similar to medication adherence, but much less important[76]. Interventions targeted to SLWH must address these issues. To address the unique needs of SLWH, we developed and piloted an intervention called WISH (Wellness Intervention for Smokers with HIV, see also Preliminary Studies). WISH builds on our prior research in motivational treatment for smoking cessation[80-82] and health behavior change among PLWH[83-90]. WISH incorporates best practice, evidence-based behavioral counseling for smoking cessation with strategies from motivational interviewing[71,91] and is delivered via phone with integrated text messaging. Participants are also encouraged to use cessation medication and advised how to do so. The goal of the intervention is to build and strengthen smokers' motivation for quitting (if not yet ready to quit) and once they are ready, to

offer best practice action oriented counseling and pharmacotherapy. But, ***to engage and retain smokers, the program is designed as a wellness intervention***, not a traditional smoking cessation program. After clarifying smokers' goals around their health and wellness, the program works with SLWH to address these goals through a multi-faceted focus on multiple (inter-related) topics relevant to their health goals, including smoking cessation, treatment adherence, mood management, substance use, etc. This approach is consistent with some of the most recent intervention development work with SLWH that addresses depressed mood in tandem with smoking cessation[92,93] or addresses medication adherence[94], but the WISH approach is relatively broader as it is based on a chronic disease wellness framed self-management approach with demonstrated acceptability among PLWH, including when delivered by phone[95-99].

Enhancement to standard care #3: Integrated phone and text counseling. Finally, WISH is delivered via mobile phone, to reduce many of the traditional barriers to care. Both phone counseling[71,100,101] and more automated or reminder-focused text messaging approaches[102,103] have been demonstrated as effective independent intervention strategies among the general smoking population, have been used to target ART adherence in other HIV populations[104,105], and mobile-phone counseling alone has been used to target SLWH who are ready to quit in the next 7 days[106]. However, *WISH is novel in using integrated text messaging as a way to foster ongoing supportive action-oriented and motivational communications between smokers and telephone counselors in between counseling sessions*. A recent study combining phone and text in a cessation program for SLWH offered the two modes in tandem, but the texts were not customized, bidirectional or integrated with phone counseling as WISH text are, and so did not independently improve cessation beyond the effect of telephone counseling[94]. Moreover, smartphone-based cessation treatments for SLWH can be feasible and engaging when offered to low SES populations, as was recently demonstrated in a feasibility/acceptability pilot with 100 men and women (81% Black; 31% Latino) drawn from a poor urban community[107]. Given the high penetration of mobile phones globally[108], particularly among lower income demographic groups, this intervention modality is particularly well suited for our geographically dispersed target population of HIV+ Veterans, and if successful, appropriate for potential adoption by existing providers of national cessation services available to VA patients.

QUALITATIVE SUPPLEMENT

The last two decades have been marked with steep increases in alcohol consumption in the U.S., which have contributed to lower overall life expectancy through increased alcohol-related liver disease mortality and other epidemics influenced by alcohol consumption (e.g., suicide and other mental-health-related outcomes). Similarly, the U.S. has observed increases in use of electronic nicotine delivery systems (ENDS), which appears to adversely influence respiratory function. Rates of non-AIDS-defining cancer deaths have also increased in recent years among PLWH, and PLWH are at greater risk for many cancers than are HIV-uninfected persons, likely as a result of the direct toxic effects of the HIV virus, as well as chronic inflammation and immune suppression/ activation, and high rates of co-infections and risk factors, including both tobacco and alcohol use. PLWH are more likely to use these substances that increase risk for cancers –alcohol and tobacco products—than persons without HIV. Additionally, PLWH experience a high prevalence of social determinants and co-occurring mental health conditions, which are likely to influence alcohol and tobacco use.

INNOVATION & IMPACT

PRIMARY INTERVENTION STUDY

This research has several innovative aspects that strengthen potential impact. First, it aims to evaluate a comprehensive, motivational wellness-based intervention for SLWH that is applicable to all smokers, not just those ready to quit. There are few large trials evaluating motivational interventions that include smokers who are ambivalent about quitting smoking, and studies conducted with SLWH are particularly lacking[51,109]. Reaching and engaging these patients in evidence-based cessation treatment has great potential for reducing disparities in care and health outcomes. Second, the study is innovative in its use of a wellness-based approach based on an Information-Motivation-Behavioral Skills Model of Smoking Cessation that our team articulated specifically for HIV+ smokers[110]. The IMB model was developed to guide HIV-related health behavior changes including prevention, adherence and engagement and in one recent study was applied to medication adherence among SLWH, but our team was the first to apply it to smoking cessation and quit attempts as the primary targets[58,83,88,94,110,111]. Third, we propose a novel approach to evaluation, applying the RE-AIM model[112] to examine the role of comorbidities and co-infections on the reach, effectiveness, adoption and implementation of an HIV smoking cessation intervention, leveraging uniquely strong and available VA clinical and health services data to do so. Our collaboration with the National VA Quitline to potentially disseminate the WISH intervention, as appropriate based on final results, is also a unique strength of the proposed project. Fourth, this study will be the first to use the VACS Index 2.0[113]to explore the impact of a smoking cessation intervention on reducing mortality risk for PLWH. This index includes expanded clinical metrics that may be particularly relevant for evaluating smokers. Fifth, we will leverage collaborations with VACS nationally and enroll PLWH receiving care in the VA system who currently smoke. These Veterans represent a high-risk population who are predominantly black, of lower socioeconomic and educational status, and have multimorbidity and increased mortality risk compared to HIV+ non-smokers. They often have a long-standing history of smoking, high levels of addiction, and are vulnerable to the negative health consequences of ongoing smoking. New interventions to decrease smoking in this population are urgently needed and can have significant impact to improve health. In sum, this research addresses an **important public health need** and is **highly responsive** to NIH goals of reducing smoking and health disparities among SLWH. If found effective, the **innovative** WISH intervention could have a meaningful **impact** on treatment for SLWH served by the largest provider of HIV care in the US and could represent a new model for intervening with SLWH.

QUALITATIVE SUPPLEMENT

The structured, standardized assessments available in survey data from the parent trial are limited for in-depth exploration of alcohol use among PLWH who smoke, as well as contexts and experiences that may influence co-occurring alcohol and tobacco use. Further, the parent study does not offer an HIV negative reference group. We therefore propose to use a qualitative investigation using a Rapid Assessment Process to explore alcohol and tobacco use, and contexts for alcohol use that may impact population risk among PLWH relative to those without HIV. Findings from this study will be highly responsive to NCI's request for new knowledge generation about alcohol and tobacco synergies that drive long-term cancer risk. The WISH trial team is well prepared to undertake the proposed supplemental study. Team members have expertise in pulmonology, alcohol- and HIV-related health services research, HIV and behavior change, and smoking cessation. Our collective experience conducting qualitative studies focused on substance use, health risk behaviors, HIV, and cancer control, as well as the outstanding data

and staffing resources will facilitate our capacity to undertake the proposed qualitative work and complete it in a 12-month period.

11.0 Objectives

PRIMARY INTERVENTION STUDY

Health disparities persist for smokers living with HIV (SLWH) relative to other smokers or to non-smokers living with HIV. People living with HIV smoke at more than twice the rate of the general population and have lower rates of cessation[12,114]. Disparities in health outcomes for SLWH include decreased immunological and viral responses to antiretroviral therapy (ART)[15,33,34,115], increased risk of non-AIDS-related cancers, infections, comorbidities and mortality[2,4,17,18,20,23-27,29,31,32,116-119]. Thus, *it is critical that SLWH quit smoking*. However, research by our team and others has shown that SLWH are largely unaware of these HIV-specific deleterious effects of smoking[40,58,110]. Additionally, our work in the Veterans Aging Cohort Study (VACS) demonstrated that Infectious Disease providers were less likely to be aware of HIV+ patients' smoking or refer them to treatment compared to general medical clinic providers[120]. While this may be in part related to few SLWH being ready to quit at any given time, interest in quitting among many SLWH is high; we have found about 70% would like to quit someday[58,72]. Unfortunately, standard care cessation services are not appealing to SLWH who are not yet ready to quit. Interventions need to be designed to enhance motivation and self-efficacy for quitting, as well as provide the support, advice, and treatment necessary for a successful quit attempt. SLWH also have other needs that may make standard care cessation services less effective[13]. For example, many SLWH have high levels of comorbid depression and substance use[40,121], particularly Veterans[72]. Cessation programs for SLWH also need to be tailored to address these needs.

We previously developed a motivational intervention targeted to SLWH called WISH (Wellness Intervention for Smokers with HIV)[122]. WISH combines HIV-specific information and skills building exercises to enhance and support smokers' motivation and self-efficacy for quitting. The counseling is designed for people at all stages of readiness to quit, not just those ready to make a quit attempt. WISH utilizes best-practice strategies from motivational interviewing and cognitive behavioral counseling[71]. To engage smokers, the program uses a comprehensive wellness approach, focusing on a range of behaviors including medication adherence, mood/stress management, other substance use and health behaviors. Once individuals are willing to make a quit attempt, they are offered action-oriented counseling. Participants are also encouraged to use first-line pharmacotherapy available through Veterans Affairs (VA) health care providers. Unlike most standard care, the program improves reach by not requiring a commitment to quit as a precondition of enrollment. This approach has been well accepted in our prior research with SLWH and others[61,81,82,122-124]. The WISH program content and tone were informed by a series of formative studies we conducted with smokers living with HIV, depressed smokers, and smokers recruited from a range of community and healthcare delivery settings[58,80,110,122,125]. Preliminary findings have all been positive and support broader testing of this approach in the proposed randomized controlled trial (RCT). We will enroll SLWH at VACS sites, leveraging our existing research infrastructure and access to a large racially and geographically diverse sample with comprehensive data on health outcomes to achieve the following **specific aims:**

1. Compare the effectiveness of WISH (an HIV-specific comprehensive wellness program designed to offer integrated phone & text counseling regardless of readiness to quit) to referral to standard evidence-based cessation services (National VA Quitline and SmokefreeVET texting program). Smokers in both arms will be encouraged to use pharmacotherapy and have access to this via the VA pharmacy. We will conduct an RCT to test the hypothesis that 7-day point

prevalence abstinence (PPA) at 6 months and presence of any 24-hour intentional quit attempt (primary outcomes), and self-reported prolonged abstinence, 7-day PPA, 30-day PPA, and change in cigarettes per day at 3 and 6 months post-randomization (secondary cessation outcomes) will be higher in WISH compared to the standard care arm. [Primary aim]

2. Describe the reach and implementation of WISH. We will assess the absolute number, proportion and representativeness (in terms of current readiness to quit, smoking history and demographic characteristics, ART use, comorbidities such as non-AIDS defining cancers, and HIV-related co-infections) of SLWH who are willing versus unwilling to enroll in the program, who do or do not use standard VA cessation services, and who use or do not use cessation medications during the study period. [Secondary aim] There are no hypotheses; this is a descriptive aim.

3. Compare cognitive-behavioral change process variables between WISH and standard care arms at 3 and 6 month follow-up. Variables will be based on the Information-Motivation-Behavioral Skills Model for Smoking Cessation (i.e., HIV specific smoking-related knowledge, motivation and self-efficacy for quitting, and cessation-related behavioral skills including cessation medication use and adherence) [Secondary aim] There are no hypotheses; this is a descriptive aim.

4. Compare markers of immune status (CD4 cell count) and mortality risk (VACS Index) between WISH and standard care at 6 and 12 months. [Secondary aim] We hypothesize that the CD4 cell counts and VACS Index scores will be improved at 12 months in the intervention patients.

If successful, this theory-based program tested with Veterans receiving care from the largest US provider of HIV services could impact reach and effectiveness of cessation services offered to all PLWH regardless of readiness to quit, reduce HIV-related disparities in smoking, and improve clinical outcomes.

QUALITATIVE SUPPLEMENT

Because the structured, standardized assessments available in survey data from the parent trial are limited for in-depth exploration, we have added a supplementary aim to the WISH trial. Further, the parent study does not offer an HIV negative reference group. We will enroll at VACS sites, leveraging our existing research infrastructure and access to a large racially and geographically diverse sample with comprehensive data on health outcomes to achieve the following **specific aim:**

5. We will qualitatively examine inter-related factors (e.g. social determinants of health, mental and other health conditions, COVID-10, etc.) and the ways in which they drive changes in substance use, as well as knowledge, beliefs and attitudes related to risks of tandem alcohol and tobacco/nicotine use. Additionally, the interview will explore whether their experiences of the novel coronavirus (COVID-19) and/or the COVID-19 pandemic have or may be impacting use or other cancer risk behaviors. This work will enable a richer understanding of how alcohol and tobacco synergies that drive long-term cancer risk are impacted by HIV, social determinants and mental health conditions, which can inform more effective interventions for high-risk populations. Further, findings could provide insight into how the COVID-19 pandemic might be impacting these already high-risk inter-related relationships among cancer risk behaviors. Findings from this qualitative supplement will yield new knowledge about alcohol and tobacco synergies that drive long-term cancer risk among PLWH relative to those without HIV.

12.0 Resources and Personnel

Recruitment and oral assent will be though the VA Puget Sound. Enrolled participants will be referred to the intervention team at Kaiser and UC Davis. Study activities at the intervention sites will collect NIH data and will be approved by the Kaiser and UC Davis IRBs.

Refer to the Multisite Supplement and Kaiser and UC Davis IRB approvals for further information regarding this relationship. Henceforth this document will refer to the research activities and protocol conducted at the VA Puget Sound unless stated otherwise.

Principal Investigator: *Kristina Crothers, MD.* Along with the other MPIs, Dr. Crothers will oversee and be responsible for all administrative and scientific aspects of project development, implementation of all policies, procedures and processes, monitoring for quality and participant safety, analyses, manuscript preparation, and dissemination of results. She will collaborate with VACS and work with the programmer at Puget Sound to identify potentially eligible participants, namely Veterans with HIV infection who currently smoke. She will work with the programmers to obtain VA electronic health record data, including comorbidities, laboratory and pharmacy data on participants. She will oversee the initial recruitment, enrollment, and randomization of participants, and the assessments of cotinine measures. She will work with the biostatisticians and the rest of the study team to analyze and interpret study data in years 4-5, and will plan activities for future dissemination working with key stakeholders within the VA. She will attend weekly all-site meetings with the other PIs, as well as conduct regular weekly meetings with the Coordinating Center team at Puget Sound.

VA Puget Sound staff

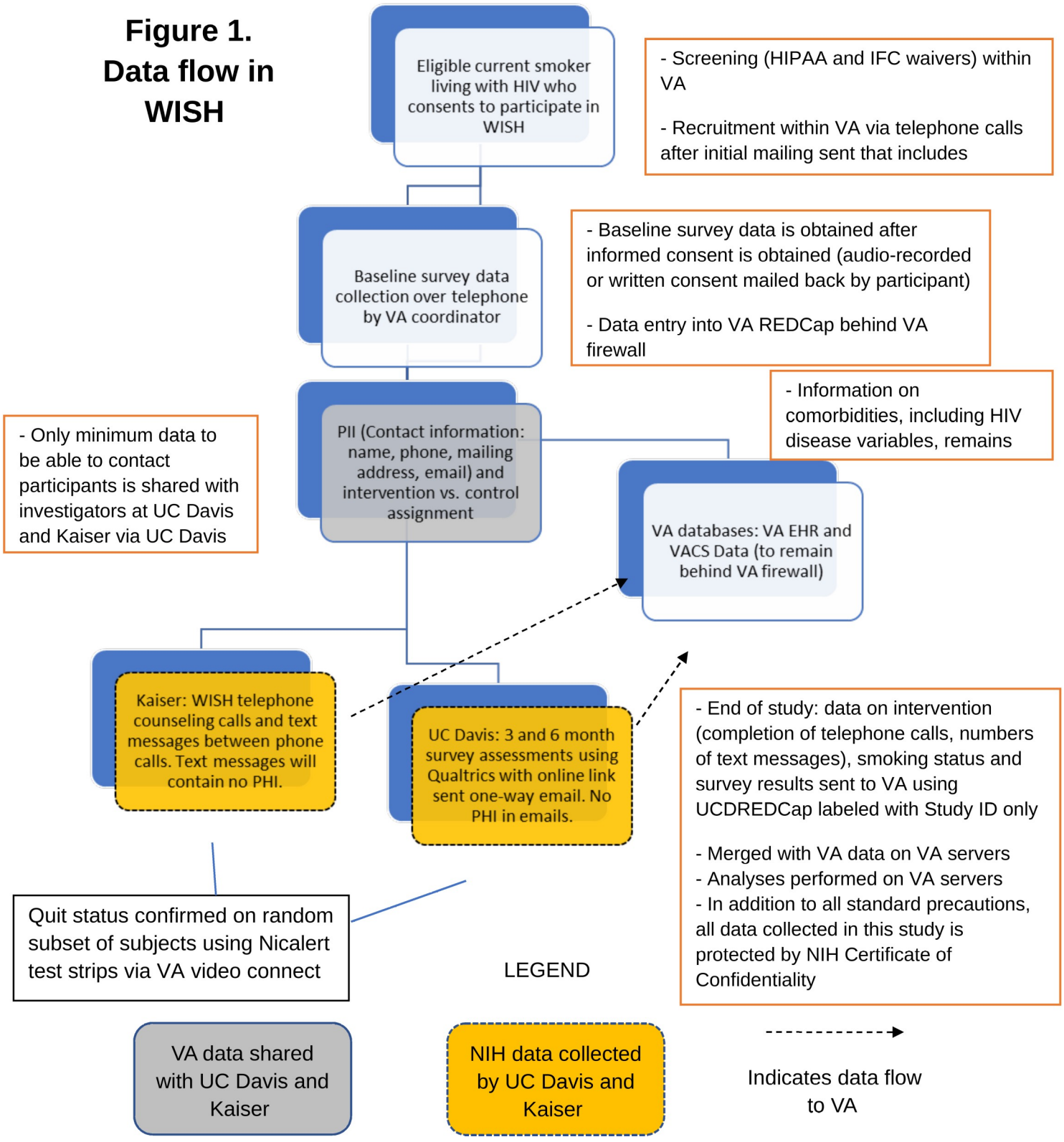
- The **Study Coordinator / Project Manager** will be responsible for overseeing and conducting patient recruitment, enrollment, and follow-up. She will complete data entry; conduct patient assessments of smoking status; maintain IRB compliance; and maintain databases.
- The **Programmer** will extract data to identify potentially eligible participant through the corporate data warehouse (CDW) and to retrieve baseline current data on comorbidities, medications, laboratory and other electronic health record data on participants. The Programmer will develop and maintain data collection and participant tracking databases. She/He will work closely with other team members to assemble data into analytic files.
- The **Analyst** / **Biostatistician** will be responsible for helping to create a study design and analysis plan that follows sound statistical principles. He will conduct statistical analyses, prepare interim and final reports, and assist with interpretation of data.
- The **Qualitative Interviewers / Analysts** will be responsible for collecting and analyzing data for the Qualitative Supplement. They will develop interview guides and conduct qualitative data collection, as well as manage all qualitative analysis, including development of templates for rapid analysis, data analysis and manuscript development and dissemination of results.

13.0 Study Procedures

5.1 Study Design

SEE DIAGRAM BELOW FOR DATA FLOW (PRIMARY INTERVENTION STUDY).

Figure 1. Data flow in WISH



STUDY & INTERVENTION DESIGN

PRIMARY INTERVENTION STUDY

First, we will randomize 20 participants to an initial Vanguard pilot trial, which will allow us to test all study implementation procedures prior to exposure of participants in the main trial, including VA video connect to test for feasibility for the cotinine dipstick quit verification later used on a random subset of subjects who report quit status at the end of the study. Then, eligible smokers who are living with HIV (n = 500) will be randomized to one of two treatment conditions: standard care control or the experimental intervention (aka, WISH) using a parallel, two-arm, randomized controlled trial and followed for one year to assess change in smoking behavior and other secondary outcomes. VA-based research activities will include recruitment, consent, randomization, data collection from VA electronic health records, and data analysis. Behavioral intervention activities and behavior change evaluation across both study arms will be conducted by non-VA sites. The data collected will be NIH data. After the intervention, data will be sent to the VA for analyses.

Standard Care Control: Control participants will be advised to quit smoking and referred to standard care treatment services provided nationally by the VHA. This includes access to a multi-call, tobacco cessation quitline program (1-855-QUIT-VET), encouragement to sign up for SmokefreeVet, an automated texting program to support cessation efforts, and access to FDA-approved pharmacotherapy for smoking cessation, provided through their local VA medical center pharmacy. Participants will be strongly encouraged to request a standard course of FDA-approved pharmacotherapy such as NRT (patch, gum, or lozenge), which is the first line smoking cessation medication within the VA, or other medication as deemed individually appropriate by their VA provider.

Experimental Intervention: Experimental participants will be offered a proactively-delivered phone-based counseling program with integrated intersession text message support delivered by the research staff at KPWHRI. Messages will be sent using Twilio, a web-based application. We cannot guarantee the security of electronic communications (security information can be found on the Twilio website https://www.twilio.com/security**)**. Public security information can be found here https://www.twilio.com/public-policy.Texts will not include sensitive health information but will be reminders about appointments and general messages to check in on your progress with your goals. Participants will also be encouraged to request a standard course of FDA-approved pharmacotherapy such as first-line NRT or other medication as deemed individually appropriate by their VA provider. Phone sessions will be recorded to ensure that the counselors are covering all topics that need to be covered in the sessions. Participant name will not be included in the recordings. Participants may refuse to have their sessions recorded. All recordings will be stored on a secure server at Kaiser Permanente and will be destroyed after data is analyzed for the study. Destruction/sanitation of research data after the project completion will be in accordance with the RCS 10-1 and Directive 6500. KPWA is a HIPAA covered entity and complies with all HIPAA regulations regarding data security. We will apply the same standard of protections to our study records. More specifically: All study files will be maintained in a centralized location on the KPWHRI departmental server. Access to this data is password protected and subject to the same security protections as other confidential health plan data. Access will be limited to staff working on this study and require access to these files. All staff are trained in appropriate security protections, computer passwords are changed on a regular basis, and all staff sign annual confidentiality agreements.

Nicalert Quit Status Confirmation: A random subset of participants reporting they have quit using nicotine products at the end of participation will receive a Nicalert test kit to complete to confirm quit status. This is a saliva test that can be completed at home. Participants will be guided through taking the test via VA video connect, a secure technological platform behind the VA firewall used by VA providers for remote consultations with patients and recently approved for research use. Pioneering this technology with a research population will contribute to innovative use of technology in research settings. See the link to VA video connect privacy here: https://mobile.va.gov/app/va-video-connect#AppFAQ. A screen shot using the snipping tool will be taken of the test strip only and stored on a secure server at the VA. The participant will not be in this screen shot. After test completion, study participants will throw the test kit and strip away.

How risks will be minimized

All aims of this study are designed to specifically minimize risks to subjects.

PRIMARY INTERVENTION STUDY

IRB Oversight. All research activities will be reviewed and approved by the IRB at each site involved in human subjects' activities: VA Puget Sound, Kaiser Permanente Washington Health Research Institute (KPWHRI), University of California, Davis (UCD), and the West Haven VA. Each IRB will ensure participants are adequately protected against risk and all research activities are HIPAA compliant.

Informed Consent. As the VA has done in prior intervention trials, we will obtain a waiver of informed consent and HIPAA Authorization from the Puget Sound VA IRB to collect and use information necessary to identify potential participants for initial study contact.

Contacted Veterans will provide verbal consent to be screened for eligibility and to participate in the study. Consent to participate will include permission to collect required study information from participants' VA and VACS records; to share the minimum necessary study relevant information among study sites/investigators; and to contact participants for the purposes of this study. Paper and electronic communications will not include reference to HIV status or sensitive health information (PHI). While we will verbally tell participants that the study is designed for smokers who are infected with HIV, the written information statements and other study materials will not refer to HIV but will only refer to "certain chronic health conditions."

Participants will be fully informed of the potential risks of participation, alternate treatment options, and their right to discontinue study participation at any time. Participants will also be free to refuse to answer any survey questions. A consent form from the University of California, Davis (UCD) will also be provided to participants regarding study procedures to occur at UCD and Kaiser Permanente (KP). Study staff at VA will not consent participants for this part of the study, Subjects will be referred to a phone number at UCD, which they are able to call with questions or concerns about the UCD consent form or study procedures conducted at those institutions. The UCD and KP are operating under single IRB procedures, and therefore UCD as lead site has administrative oversight over KP's study procedures. Study staff at UCD have been granted a waiver of documentation of consent.

Internet. **Any activity on the internet involves risk and, in using your own computer, you should take the normal precautions of ensuring that your system is running the most current version of your browsing software, that you have up-to-date virus protection, and that you implement a software or hardware firewall to protect your computer and yourself. If you choose to use a public computer to access this resource (such as a library**

computer), know that your information is only as safe as that computer's safety features. Any website can be hacked. By ensuring your computer has up-to-date security measures, you can reduce the risk to yourself, but risk cannot be totally eliminated.

Breach of confidentiality. We will implement and strictly adhere to multiple measures designed to protect participant confidentiality and ensure data security. Each level of data security is described below in Section 7.0 Privacy and Confidentiality. As a result of these measures, we do not expect any invasion of privacy or breach of confidentiality for any patient included in this project.

QUALITATIVE SUPPLEMENT

IRB Oversight. All research activities will be reviewed and approved by the IRB at the VA Puget Sound, which will ensure participants are adequately protected against risk.

Informed Consent. We will obtain a waiver of informed consent and HIPAA Authorization from the Puget Sound VA IRB to collect and use information necessary to identify potential participants for initial study contact to recruit for interviews.

Contacted Veterans will be screened for eligibility and provide verbal consent to participate in the study. If eligible, they will provide verbal consent, and the conversation will either be recorded as a means of documenting informed consent or participants may opt to send back a signed consent if they do not wish to be recorded. Consent to participate will include permission to record qualitative interviews and is separate from the consent process for the Primary Intervention. Paper and electronic communications will not include reference to HIV status. All written information statements and other study materials will not refer to HIV but will only refer to "certain chronic health conditions."

Participants will be fully informed of the potential risks of participation and their right to discontinue study participation at any time. Participants will also be free to refuse to answer any interview questions.

Breach of confidentiality. We will implement and strictly adhere to multiple measures designed to protect participant confidentiality and ensure data security. Each level of data security is described below in Section 7.0 Privacy and Confidentiality. As a result of these measures, we do not expect any invasion of privacy or breach of confidentiality for any patient included in the Qualitative Supplement.

Potential Risks: The potential risks for the Qualitative Supplement include those that may result from potential psychosocial distress or discomfort resulting from discussion of health status, health behaviors and desired health care communication and support. Additional risks include those related to invasion of privacy or breach of confidentiality. To minimize these risks, we will implement and strictly adhere to several security measures designed to protect participant confidentiality and ensure data security, described below in Sections 7 and 9. As a result of these measures, we do not expect any invasion of privacy or breach of confidentiality for any data included in this project and believe all risks involved with the study are minimal. To minimize stress and discomfort, participants will be able to decline to answer questions they wish and will be free to discontinue the interview at any time.

Potential Benefit of Research to the Subject and Others

PRIMARY INTERVENTION STUDY

Participants may benefit from this study. All participants may receive some satisfaction or indirect benefit from contributing to this research designed to encourage people living with HIV to quit smoking. Additional benefits include assistance quitting smoking. Participants in the WISH intervention may also benefit from other positive health behavior changes instigated by participation in this wellness intervention. Participants who stop smoking may experience reduced disease risk and potentially better management of existing chronic conditions, including HIV infection.

Society may benefit from this study. Study results will provide critical information about the comparative effectiveness of a wellness-based smoking cessation intervention designed for SLWH versus referral to standard care services available to Veterans. If the intervention is found to be effective, it could be disseminated nationwide through the National VA Quitline, thereby reducing smoking prevalence and improving health outcomes among the largest patient population of smokers living with HIV in the country. If effective, WISH could also be rolled out to other Veterans through the National VA Quitline, helping to expand the reach and effectiveness of cessation interventions offered to all Veterans in this country. The study will leverage existing VA data resources to expand knowledge about how to reduce disparities in smoking rates, uptake of cessation services and associated clinical health outcomes for SLWH.

QUALITATIVE SUPPLEMENT

Participants enrolled in the Qualitative Supplement may benefit from this research directly and indirectly. The interviewers in this study have a breadth of experience interviewing VA patients, and report that VA patients are often eager to share their personal experiences. This study may provide patients an important outlet for communicating their experiences and the opportunity to gain satisfaction from participating in a research project designed to increase understanding of Veteran experiences with alcohol use, tobacco use and key social determinants of substance use, mental health and cancer outcomes and thus inform intervention development.

In addition, we believe the potential to contribute to scientific knowledge outweighs the minimal risks to these subjects. Persons living with HIV (PWWH) are more likely than those without HIV to use both alcohol and tobacco products, to have alcohol- and tobacco-related cancers, and to experience key social determinants of substance use, mental health, and cancer outcomes. Veterans – especially those living with HIV – also experience a high prevalence of social determinants of health and co-occurring mental health conditions, which are likely to influence alcohol and tobacco use. The proposed supplement will enable a richer understanding of how alcohol and tobacco synergies that drive long-term cancer risk are impacted by HIV, social determinants and mental health conditions, which can inform more effective interventions for high-risk populations.

5.2 Recruitment Methods

PRIMARY INTERVENTION STUDY

Number of subjects: This study will enroll 520 participants.

PARTICIPANTS AND RECRUITMENT

Veterans who are HIV+ and are current smokers will be recruited by study staff at the VA Medical Center-Puget Sound from the 9 VA medical centers participating in the Veterans Aging Cohort Study (VACS). Participants will be identified from the VACS cohort and the broader sample of HIV+ patients treated at these 9 medical centers; about 2,000 smokers. As needed, recruitment will be expanded to include eligible patients from the larger national cohort of HIV+ Veterans treated in the entire VHA system; about 8,000 smokers.

Potentially eligible Veterans will be identified using VACS data and medical records from the VA corporate data warehouse (CDW). HIV+ current smokers who do not have documented exclusions (e.g., dementia, cognitive impairment) will be mailed a study invitation letter (Attachment A Invitation Letter) and contacted by phone, if they do not opt out of contact by returning an opt-out card that will be included with the study invitation letter or calling the number provided. The mailing will also include a study flyer describing the study (Attachment B Flyer) ,the study information sheet (Attachment C Information Statement) for the VA study procedures, and the information sheet for study procedures conducted at UCD and KP. Interested individuals will be screened by phone (Attachment D Recruitment Script). If eligible, they will provide verbal consent, and the conversation will either be recorded as a means of documenting informed consent or participants may opt to send back a signed consent if they do not wish to be recorded, and complete a baseline assessment (Attachment E Baseline Questionnaire) prior to randomization. Participants who cannot complete the baseline survey at the time of the initial call, and who do not follow-up to complete this survey will be called up to but not exceeding 3 additional times and mailed a letter (Attachment F Enrollment Letter) asking them to complete the survey if they do not respond.

Materials to be used: Study Invitation Letter, Flyer and Information Statement; Recruitment Script

Participant Compensation: $20 for each of 3 surveys (baseline, 3-, 6-months post-enrollment). Participants should expect to receive their check via mail approximately 8-12 weeks after their completion of each survey. The VA will issue payment for the baseline survey. As the follow-up surveys are being completed by UCD, they will issue payment for the 3 and 6 month surveys.

QUALITATIVE SUPPLEMENT

Number of subjects: The qualitative supplement will enroll up to 80 participants; up to 40 with an HIV diagnosis and up to 40 without an HIV diagnosis.

PARTICIPANTS AND RECRUITMENT

Veterans who have screening measures documented in the EHR in the past two years that indicate use of alcohol and cigarettes or ENDS and are living with HIV will be eligible; half of enrolled participants will NOT have an HIV diagnosis. Participants will be recruited by study staff at the VA Medical Center-Puget Sound from the VA nationally. The sample will purposively include patients drawn from a range of geographic areas, diverse demographic characteristics (age, sex, race/ethnicity) and with histories of heavy/light drinking patterns and heavy/light smoking patterns (based on VA electronic records of routine Health Factors and AUDIT-C assessments). The sample will be matched in 5-year blocks of age, gender race/ethnicity and activity within the VA in the same fiscal year given we plan to enroll participants with and without an HIV diagnosis. Exclusion criteria include pregnancy, hospice enrollment, cognitive impairment, unstable medical or physical conditions, and lack of telephone access. This qualitative supplement is *not* limited to veterans living with HIV.

Potentially eligible Veterans will be identified using medical records from the VA corporate data warehouse (CDW) and will be mailed a study invitation letter and study information statement with a phone number/post card to opt out; those who do not opt out in two weeks will be called to assess interest in participating. Project staff will make a total of 3 calls to each listed number before deeming participants not interested. We will retain a list of individuals of who were deemed not interested, either due to calling to inform us, sending the opt-out postcard or non-response to recruitment calls, so that we do not re-contact them. Recruitment will continue until an adequate sample is interviewed and we reach saturation. We anticipate that we will need to examine 800-1000 patient records to enroll approximately 100 Veterans (50 with an HIV diagnosis and 50 without) in order to interview approximately 80 Veterans (40 with an HIV diagnosis and 40 without), given than some may drop out after enrollment but before the interview.

Materials to be used: Recruitment letter; Opt-Out Postcard, Supplement Information Statement; Recruitment Script; Screening Script

Participant Compensation: Participants will be compensated $40 for a qualitative interview lasting between 60-90 minutes. This reimbursement will be made by check from the Seattle Institute for Biomedical and Clinical Research (SIBCR) and will be mailed to you up to 6−8 weeks after each visit. To comply with Internal Revenue Service (IRS) guidelines, we will collect your social security number. You may receive an IRS Form 1099.

5.3 Informed Consent Procedures

PRIMARY INTERVENTION STUDY

We are requesting a Waiver of Informed Consent and HIPAA Authorization from the Puget Sound VA IRB to collect and use information necessary to identify potential participants for recruitment.

We are requesting a Waiver of Documentation of Informed Consent for study participation. Interested Veterans will provide verbal consent to be screened for eligibility and to participate in the study. During the oral assent process, research staff will answer all questions about study participation and ensure that the participant understands the decision to enroll in the voluntary study. Participants are informed that they may elect not to participate in any study activities and that they may cease participation in the study at any time.

All study personnel will be current with required VA trainings and will remain in compliance with these trainings throughout the study period.

QUALITATIVE SUPPLEMENT

We are requesting a Waiver of Informed Consent and HIPAA Authorization from the Puget Sound VA IRB to collect and use information necessary to identify potential participants for recruitment and screening.

Interested Veterans will provide verbal consent to participate in the qualitative interview which will be documented by audio recording. If participants opt out of recording, they will be offered

the option to receive a consent form with a pre-paid return address that they can review, sign and return prior to enrolling in the study.

The initial recruitment invitation sent to all participants will also include a study information statement describing the study. Interested individuals will be screened by phone. If eligible, they will be asked to provide verbal consent. This consent is separate from consent for the Primary Intervention. During the verbal consent process, research staff will answer all questions about study participation and ensure that the participant understands the decision to enroll in the voluntary study. Participants are informed that they may elect not to participate in any study activities and that they may cease participation in the study at any time. After verbal consent, participants will be offered the option of completing the interview at this point, or scheduling a time in the future to complete the interview. Prior to beginning the interview research staff will ask for verbal confirmation that they have participant permission to record the interview. In the event that the participant declines to have the conversation recorded but still consents to participate, the interviewer will not record the interview but will take detailed notes on the conversation that can later be used for analysis.

All study personnel will be current with required VA trainings and will remain in compliance with these trainings throughout the study period.

Materials to be used: Information statement; Recruitment script; Verbal consent script; Screening script

5.4 Inclusion/Exclusion Criteria

PRIMARY INTERVENTION

Inclusion criteria:

- In care in the VA
- HIV+ serostatus
- Currently smoking ≥ 5 cigarettes daily
- Access to cell phone with text messaging capabilities
- English speaking

Exclusion criteria:

- Psychosis, dementia or significant cognitive impairment documented in the EHR
- Documented or observed hearing or comprehension difficulties that would preclude participation in study telephone calls
- Currently receiving cessation counseling or using an FDA approved treatment to quit smoking
- Institutionalized or imprisoned
- Pregnant

QUALITATIVE SUPPLEMENT

Inclusion criteria:

- In care in the VA
- Documentation of tobacco/nicotine use (including none) via Health Factors
- Documentation of alcohol use (including none) via the AUDIT-C
- English speaking

Exclusion criteria:

- Under age 18
- Pregnancy
- Hospice enrollment
- Psychosis, dementia or significant cognitive impairment documented in the EHR
- Lack of telephone access

5.5 Study Evaluations

PRIMARY INTERVENTION STUDY

Screening. Potentially eligible individuals will be identified using the VACS and CDW automated records which Dr. Crothers has access to within the VA. Individuals will be selected for contact after initial screening for their HIV status, smoking status, and lack of excluded medical conditions (e.g., no psychosis, dementia or cognitive impairment).
Persons who do not opt out of further contact will be called in about a one to two weeks after the initial mailing is sent to determine interest and eligibility, by asking questions detailed in the Patient Recruitment Script (Attachment D Recruitment Script). Individuals who are determined to be eligible and provide consent will then be asked to complete a baseline survey (described below, Attachment E) via telephone.

Survey Assessments. Assessment items include standard, validated measures. The first assessment will be conducted prior to randomization (Attachment E Baseline Survey). Smoking level will be used to establish study eligibility and to block randomize participants in addition to other criteria. To describe both arms, we will also assess *demographics* (e.g., age, race/ethnicity, sex, gender identity, sexual orientation, education, employment, income, service-connected disability, current living situation), *tobacco and nicotine use history* (cigarettes per day, years smoked, use of other tobacco and nicotine products including e-cigarettes, history of quit attempts in past year assessed with CDC BRFSS items), *nicotine dependence* (assessed with the Fagerstrom Test of Nicotine Dependence[126]) and *cessation treatment history*.

Assessments after the intervention will be conducted by the UC Davis research staff at 3 months (end of treatment) and also 6 months post-randomization in both arms. We will assess 12-month outcomes through VA EHR data that will include documented smoking status, and immune markers and VACS index scores for Aim 4 analyses. This allows us to assess intermediate IMB model constructs and abstinence/ quit attempt outcomes at the end of scheduled treatment, at the primary follow-up of interest at 6 months, and to have long-term follow-up for smoking related, HIV-related and service-related outcomes over a year study period. Interviewers will be blinded to intervention assignment. Each will be intentionally brief to enhance response and participants will receive a $20 incentive for completion.

Cognitive-behavioral change process measures consistent with an IMB framework will be assessed as follows**:** *HIV-Specific Smoking Knowledge* will be assessed using items validated in a survey of SLWH conducted by the study team[58]. We will assess *Self-efficacy (*for quitting smoking, reducing smoking, and for specific behavioral skills such as managing cravings, and stimulus control) using 10 point Likert scales for each construct, and *Motivation for quitting* (assessed by rating on a 1-10 Likert scale recommended by OBSSR's Behavior Change Consortium). *Nicotine Withdrawal Symptom Management* will be assessed with the self-report Minnesota Smoking Withdrawal Scale, Revised[127,128], which reliably measures symptom increases associated with cessation of nicotine intake and symptom alleviation associated with nicotine replacement[129].

A brief *Substance Use* battery includes the AUDIT-C alcohol screening measure[130], DAST-10 screening measure for illicit drug use and marijuana use [131], and 2 injection drug use history items (ever in past and 3-month use)[132]. *Depression* will be assessed with the 8-item version of the PHQ-9[133,134] that excludes the suicide item.

At each *follow-up*, we will re-assess baseline measures subject to change (e.g., cessation-related Information, motivation and behavioral skills; depression; substance use) and the measures described below:

Smoking abstinence and quit attempts: To facilitate comparison of treatment effects with other published trials, the primary outcome of 7-day PPA will be assessed at 6 month follow-up by self-report. As is appropriate for a motivational intervention trial that enrolls participants regardless of readiness to quit, the presence of any quit attempt by 6 months following randomization will also be a primary outcome[135]. This BRFSS item[136] reflects both abstinence (all abstainers will have made a serious quit attempt) and motivation to quit smoking (persons truly motivated to quit will make a serious quit attempt) and is more appropriate than abstinence for participants not interested in quitting prior to enrolling in the intervention. Secondary smoking-related outcomes will include measures of 7-day and 30-day PPA, each assessed as a self-report of no smoking – even a puff – during each timeframe[137]; number of cigarettes smoked per day; and floating prolonged abstinence (a proxy for sustained abstinence appropriate for evaluating a motivational intervention, in which the start point "floats" based on one's actual quit date rather than a pre-defined target quit date)[138] at 3 and 6 months, and the number and duration of quit attempts and presence of any quit attempt at all follow-ups. For subjects reporting quit status, a random sample of 20% of these subjects will receive a saliva test kit in the mail to verify quit status. The subject will meet with research staff via VA video connect, which is approved for research use, and will take the saliva test while a VA staff member watches to verify identity and correct test completion. During the time it takes for the test to show a result (15-30 minutes), staff will ask additional questions about nicotine exposure and qualitative questions about their experience being in the study. When the test shows a result, VA research staff will use the snipping tool available on VA computers to take a screen shot of the image of the test strip. The subject will be instructed to stay out of the video shot while the strip is held up so that the picture is only of the test strip. There are no identifying marks on the test strip, including no mention of nicotine, HIV status, personal information, or other identifiable markings. The screen shot will be saved on the secure server behind the VA firewall in a separate folder available only to approved staff. The picture will be saved with only the study ID listed and no other identifying information listed. Pictures will be deleted at the same time as other identifiable study data links. *Cessation medication use and adherence*: We will monitor use of NRT and other FDA-approved cessation medications (i.e., varenicline, bupropion) using both *self-report* and *electronic VA pharmacy records* (e.g., medication used, number of refills, days of therapeutic coverage dispensed). We will take advantage of VA's robust pharmacy and claims data to confirm NRT or other pharmacy refills. While NRT is the first-line and most prevalent cessation medication used in the VA, by monitoring all cessation medications, we will be able to understand if participants used/ switched to a different cessation medication during the study period vs. not using/ discontinuing treatment altogether. This will also allow us to describe the total days used of any cessation medication as an aggregate measure of adherence in addition to NRT total days. We will first assess total number of days each medication was used during the study period by relying on pharmacy records and adjust based on self-report as appropriate[139]. For example, if one received a 60-day supply of medication but reported only taking it 40 days, we will code as 40 days use; if one reports 60 days of use but only received 30-days, we will code this as 30 days use.

Other usual care treatment utilization: Utilization of behavioral treatments explicitly and not explicitly recommended or referred through the study will be assessed by self-report and automated records to characterize use of usual care cessation services.

Additional data will be collected from VACS, including most recent *CD4 count, VACS Index 2.0 of mortality risk* (based on weighted and combined routine clinical measures)[140-142], most recent *HIV RNA level*, current *antiretroviral medication prescribed, and antiretroviral adherence* (therapeutic coverage past 6 months) will be assessed at baseline and 6 and 12 months. We also use the VACS database to describe *HIV-related co-infections (e.g., HPV; Hep B & C);* and relevant *comorbidities* (e.g., COPD; non-AIDS defining cancers including lung, anal, Hodgkin lymphoma) at baseline and during the year study period.

QUALITATIVE SUPPLEMENT

Screening. Potentially eligible individuals will be identified using the CDW. Individuals will be selected for contact by mail after initial screening in CDW data to identify whether they have routinely collected screening measures documented in the CDW within the past two years for use of alcohol and cigarettes or ENDS. Additionally, initial screening in CDW data will identify lack of excluded medical conditions (e.g., no psychosis, dementia or cognitive impairment). Persons who do not opt out of further contact will be called a minimum of two weeks after the initial mailing is sent to determine interest and eligibility, which will be done by asking questions detailed in the Patient Recruitment Script. Individuals who are determined to be eligible based on phone screening questions and subsequently provide verbal consent will be asked to complete a qualitative interview (described below) via telephone or Microsoft Teams.

Qualitative Interviews. Qualitative interviews will be conducted to elicit information regarding the co-occurrence and inter-relatedness of alcohol and tobacco use, as well as the sociocultural context for alcohol and smoking that may place them at higher near-term health and mental health risks and higher long-term cancer risks. Interview guides for these semi-structured individual interviews will contain open-ended questions and areas to query, detailed in the Qualitative Supplement Interview Guide. Main thematic domains the interviews will cover include: (a) participant demographics, (b) substance use history and recent changes in substance use, (c) explanatory model of social determinants of health and mental health to uncover drivers of changing substance use, particularly changes in alcohol, cigarettes and ENDS, (d) knowledge, beliefs and attitudes related to near-term health and mental health risks and long-term cancer risks of substance use, particularly tandem alcohol and tobacco/ nicotine use; and (e) their experience of the novel coronavirus (COVID-19) and whether cancer risk behaviors have been influenced by COVID-19 experiences. We will iteratively modify queries in the guide if during initial coding a theme emerges that requires further exploration.

All qualitative interviews with participants will be conducted and recorded using 1 of 2 VA-approved recording options: Microsoft Teams, which can save audio files directly onto the secure drive, or with VA-approved, encrypted digital recorders which will record interviews from a speaker phone in a private room. During the COVID-19 pandemic, study staff will use personal phones with the caller ID number blocked to recruit and conduct phone interviews from home, in alignment with guidance from ORD stating that personal phones can be used to conduct research. Interviews that are digitally recorded will be recorded with VA-approved, encrypted digital recorders and stored in a secure, locked location. As applicable due to COVID-19 practices, recordings will then be transported (with authorization to transport sensitive information) back to VA Puget Sound. All research staff conducting interviews off-site will have an approved Authorization to Transport Sensitive Information. Recordings will be uploaded to a password-protected folder on a secure server. Digital recorders will be kept in a locked, secure location when not in use. Digital recorders will be sanitized when no longer needed for the study. Each participant will be compensated $40.

5.6 Data Analysis

PRIMARY INTERVENTION STUDY

Sample Size and Power. With a sample of 500, we will have at least 80% power to detect a clinically important difference between the intervention arm and the control arm on our primary study endpoints of 7-day point prevalence abstinence at 6 months and the occurrence of any quit attempts, also assessed at 6 months. By convention[143], we will impute that non-responders are smoking (or had no quit attempts), so there will be 250 per group in the intent-to-treat follow-up analyses for these two primary outcomes. Allowing for 20% attrition at 6-month follow-up (the primary endpoint of interest), the responder-only analytic sample will include approximately 200 per group (N=400) for all self-reported outcomes, which is still sufficient to detect a clinically significant difference of 10% at 80% power (see table below).

We computed effects detectable for this sample size assuming a two-sided, .05 significance test and used the normal approximation to the chi-square without continuity correction[144]. The exact difference between control and intervention groups which is detectable with 80% power depends on the rate of smoking cessation in the control group. Based on rates obtained in prior research with HIV+ smokers and uptake rates of smokers referred to standard cessation counseling services, we expect that the rate in the control group for 7-day PPA will be 10%[51,124,145,146]. In prior research with SLWH, Lloyd-Richardson and colleagues [51] found 10% of SLWH were abstinent at 6 months after receiving either self-help + NRT or a motivationally enhanced counseling program + NRT. Humfleet et al.[38] reported 7-day PPA rates of 15% at 6 months among SLWH provided brief counseling + NRT and 27% among participants receiving a computer-based program modelled on the standard self-help provided to controls + NRT. This suggests intervention can be effective among SWLH, increasing abstinence rates by more than 10% and that standard cessation may result in ~10% abstinent at 6 months. We used this to establish our expected abstinence base rate. This rate also reflects the fact that many controls will opt not to receive the cessation services available. We will have 80% power to detect a 10.0% intervention effect (confirmed 7-day PPA: 10% control vs. 20% intervention, OR=2.25), as shown in the table below.

Outcome	Base Rate	Intervention Rate	Sample Needed Per Arm for 80% Power
7-Day Abstinence at Month 6	10%	17%	373
	10%	18%	295
	10%	19%	**240**
	10%	20%	**199**

We expect 20% to 25% of controls will have an intentional quit attempt. If 20%, the difference detectable with 80% power will be 12.3% (20% vs. 32.3%), OR=1.91; if the control rate is 25%, it will be 13.0%.

Data Analyses. All analyses will use an intent-to-treat (ITT) approach. Individuals will be analyzed by randomization group regardless of their utilization of assigned treatments. All analyses will be performed using the R statistical computing environment (https://www.R-project.org/). Robust sandwich-style standard errors will be used to account for potential violations of the model-based variance structures for linear and Poisson regressions. Confidence intervals for parameter estimates will be based on a confidence level of 95%. Hypothesis tests will be double-sided and based on a significance level of 0.05.

Aim 1. Compare the effectiveness of experimental and control arms by comparing 7-day PPA at 6 months, and patient reported 24-hour intentional quit attempts, prolonged abstinence, 7-day PPA, 30-day PAA, cigarettes smoked per day, at 3 and 6 months post-randomization.

Analyses of Primary Smoking-Related Outcomes. We will first use chi-square analyses to compare the percentages in the control and intervention groups who are abstinent by the confirmed 7-day PPA intent-to-treat measure. We will then repeat these analyses using logistic regression to control for the four baseline variables which we used in the block randomization (recruitment site, baseline intention to quit within 30 days, number of cigarettes smoked per day <10, sex), since failure to do so can result in biased estimates of the treatment odds ratio. In addition, we will fit a second adjusted model which adjusts for these stratification variables. In all of these analyses, anyone with missing data on smoking status at follow-up will be assumed to be smoking. Following the Russel Standard,[143] unless deceased, respondents who are missing PPA outcome data will be classified as smokers in the primary analysis. If missingness is non-differential between treatment arms, classifying non-responders as smokers will tend to produce a conservative effect estimate biased towards the null hypothesis of no difference between intervention groups. In the Dropout Analyses section, we describe alternative approaches we will use to examine the sensitivity of our estimates to this assumption.

For the outcome of 24-hour quit attempts post randomization, we will analyze this outcome both as a binary measure (none vs. 1+ attempts) and as a count type variable. For the binary measure, we will do unadjusted chi-square tests and adjusted analyses using the same two logistic models described above with the addition to the models of baseline number of quit attempts in the prior year. For the count version of this measure, we will compare mean number of quit attempts in the groups using t-tests/Wilcoxon tests (unadjusted analyses). For the adjusted analysis we will fit the same two models using either ordinary least-squares regression or Poisson regression (choice will depend on the shape of the distribution for the number of attempts). When smoking status is unknown or the quit attempt question is not answered, we will assume that the person made no quit attempts.

Analyses of Secondary Smoking-Related Outcomes. Analyses of number of cigarettes smoked per day, self-report PPA, and floating prolonged abstinence outcomes will be done in a similar manner to that used for the primary smoking outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). We will use regression modeling to examine the effect of the intervention over the entire course of follow-up, using generalized estimating equations (GEE) to account for the within-subject correlation over time. We will quantify a potential non-constant intervention effect over time using interaction terms. If there is sufficient evidence of a non-constant intervention effect, we will use month 6 follow-up as the primary time point of interest. Otherwise we will use the GEE regression model to estimate the effect of intervention using the entirety of the follow-up data.

Aim 2. Describe the reach and implementation of the HIV-specific comprehensive intervention.
Descriptive and bivariate analyses will be used to characterize absolute number, proportion and representativeness (in terms of current readiness to quit, smoking history and demographic characteristics, antiretroviral use, comorbidities such as non-AIDS defining cancers, and HIV-related co-infections) of smokers living with HIV who are willing versus unwilling to enroll in the program, who do or do not enroll in standard VA cessation services, and who use or do not use NRT or other cessation medications during the study period. Group comparisons will be made using t-tests or Wilcoxon-Mann-Whitney non-parametric tests for continuous/ ordinal variables and chi-square for binary outcomes. In addition, we will use multiple regression models to explore how predictive these factors are in combination of willingness to enroll, utilization of VA standard cessation services, and use of cessation medications.

Aim 3. Compare cognitive-behavioral change process variables based on the Information-Motivation-Behavioral Skills Model for Smoking Cessation (i.e., HIV specific smoking-related knowledge, self-efficacy for quitting or reducing smoking, motivation to quit, and cessation-related behavioral skills including cessation medication use/ adherence) between the experimental and control arms at 3 and 6 month follow-up.

Analyses of intermediate change process outcomes will be done in a similar manner to that used for the smoking -related outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). For outcomes such as self-efficacy, adjusted models will always include the baseline measure of the outcome under analysis (note, we cannot do this for cessation since 100% are smoking at baseline). We expect to use least squares regression to analyze HIV-specific smoking knowledge, motivation to quit, self-efficacy for quitting and reducing smoking, and cessation-related behavioral skills, (possibly after a transformation to account for possible left or right skewness). We will use a similar approach to evaluate NRT and/or other cessation medication use and adherence. We will also test if the effect of the intervention is constant across the three follow-ups using GEE.

Aim 4. Compare CD4 T-cell count and VACS Index of mortality risk between arms at 6 and 12 months.

Analyses of secondary HIV-related outcomes will be done in a similar manner to that used for the primary and other secondary outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). For outcomes such as CD4 count and VACS Index, adjusted models will always include the baseline measure of the outcome under analysis.

The VACS Index is a validated, generalizable risk index for predicting all-cause mortality that uses routine clinical laboratory data[142,147]. We will compute the VACS Index 2.0 version based on the following variables obtained from the VACS database that are also in the original 1.0 version: age, CD4, HIV-1 RNA, hemoglobin, alanine and aspartate transaminases, platelets, creatinine and hepatitis C virus serostatus, along with the new variables of albumin, white blood count, and body mass index in the 2.0 version that improve discrimination for mortality[113]. Each 5-point increase in VACS Index 2.0 score reflects an approximate 1.3-fold increase in mortality, and preliminary analysis suggests scores are higher among current smokers compared to former or never smokers[113]. We will test the hypothesis that participants randomized to the intervention arm will experience a greater reduction in VACS Index 2.0 scores over 6-12 months compared to

the control arm, potentially due to smoking reduction, smoking cessation and/or other wellness focused changes in behavior that may be reflected in the biomarkers of the Index.

Dropout Analyses. The Russel Standard of counting non-responders as continued smokers is appealing as a way to ensure uniformity in the handling of missing data in smoking cessation studies. However, it is difficult to justify statistically, and its impact on the scientific conclusions of a study must be considered. To this end, we propose to perform a thorough investigation of the impact of the "missing = smoker" assumption by considering several different statistical approaches to handling non-response. Estimates of the effect of the intervention under these alternative specifications of the missing data mechanism will be compared to the estimates obtained using the "missing = smoker" assumption to see how sensitive our results are to this assumption.

The "missing = smoker" assumption is a form of deterministic imputation that can affect p-values and confidence intervals by artificially reducing the variance of the data[148]. To address this shortcoming, we will repeat the analyses of our primary outcomes using less deterministic imputation procedures. We will examine patterns of missingness in the two intervention arms to determine to what degree non-response differs between the two arms and to determine relevant baseline characteristics that are related to non-response. We expect variables such as readiness to quit and level of nicotine dependence to be important factors in these models, but other baseline variables may be included as well. We will then use these baseline measures to construct imputation models for the missing responses. Multiple imputation procedures will be used to correctly account for the uncertainty in imputed values, resulting in valid p-values and confidence intervals. First, we will refit the regression models described in the previous aims using the imputed data to obtain estimates of the effect of the intervention consistent with a Missing at Random non-response model. Then, we will conduct sensitivity analyses under the assumption of non-ignorable non-response, also referred to as Missing Not at Random[149]. As noted in Hedeker[148], the Russel Standard of counting all non-responders as continued smokers is itself a form of non-ignorable non-response, in that it assumes a direct relationship between missing status and the unobserved outcome. Since assumptions regarding non-ignorable non-response cannot be checked using the observed data, it is important to consider alternative specifications for these types of models. To achieve this, we will use a 2-step GEE imputation method[149]. This method provides a flexible and transparent approach to handling non-ignorable missingness that improves upon the Russel Standard both by accounting for the uncertainty of the imputation method when calculating standard errors as well as by incorporating available covariate information.

QUALITATIVE SUPPLEMENT

Sample Size and Power. The overall sample (N ~ 80) is within the recommended size parameters for elicitation research and should be sufficient to achieve thematic saturation for specific subgroups of interest, such as HIV-positive and HIV-negative Veterans (n=40 each). We anticipate a loss to follow up rate of 20%, and thus aim to approach approximately 100 Veterans. Recruitment will continue until an adequate sample is interviewed and we reach saturation.

Data Analyses. Data will be analyzed using a Rapid Assessment Process in which transcribed responses will be summarized into a matrix (respondent X domain/question), matrices will be reviewed to generate memos, and memos will be used to summarize themes/domains. For all interviews, matrices will be independently derived by two analysts and cross-checked by Dr. Williams in an iterative fashion (e.g., after completion of 6) to make needed adaptations as themes requiring additional exploration arise. Once all data are collected, themes will be

summarized, and prototypical examples will be used for illustration. As needed, secondary coding will be done using password-protected Atlas.ti software.

5.7 Withdrawal of Subjects

PRIMARY INTERVENTION STUDY

Participants may withdraw voluntarily from the study at any time. The participant will be disenrolled and will not participate in any further study activities. Dr. Crothers and the study sponsor may still use information that was collected prior to the subject's withdrawal, unless the participant submits a written request to have their data withdrawn.

QUALITATIVE SUPPLEMENT

Participants may withdraw voluntarily from the study at any time. The participant will be disenrolled and the qualitative interview would end immediately. The investigators and the study sponsor may still use any qualitative data that was collected prior to withdrawal, unless the participant submits a written request to have their data withdrawn.

14.0 Reporting

PRIMARY INTERVENTION STUDY

If a serious adverse event (SAE) occurs, the PI will follow the policy and procedures established by the IRB. Specifically, the PI will report all SAEs to the IRB and local Research and Development (R&D) Office within five working days. SAEs will be reported even if the PI believes that the adverse events are unrelated to the protocol. In the event a study participant reports a SAE to a research team member, the team member will contact the PI. Problems/adverse events that are not serious that are related to the protocol will be reported to the IRB within 10 working days. All SAEs and problems (anticipated/expected or not) will be kept in a log.

While research staff will do their best to adhere to IRB approved research protocols, in the event that a protocol deviation is noted, action will be taken to rectify the protocol deviation. If research staff becomes aware of a protocol deviation, violation or noncompliance, the event will be reported to the IRB and all necessary reporting agencies within acceptable reporting requirements. Non-serious deviations will be reported on the next CRQ.

QUALITATIVE SUPPLEMENT

We do not anticipate any serious adverse events to occur as this research activity poses minimal risk to subjects. However, any and all unanticipated problems, serious adverse events and protocol deviations will be recorded and reported immediately to the study Principal Investigator. The Principal Investigator will be the monitoring entity responsible for ensuring that all measures related to data security and protection of subject privacy and confidentiality are being followed. The Principal Investigator will ensure that the ISO and Privacy Officer are notified within one hour of any improper use or disclosure of study data. Any serious adverse events and/or serious problems will be reported to the IRB within 5 business days.

15.0 Privacy and Confidentiality

PRIMARY INTERVENTION STUDY

PHI will be obtained during the course of the study.

Breach of confidentiality. Multiple steps will be taken to protect participant confidentiality. Each level of data security is described below.

6. *Data storage*. VA, UCD, and KPWHRI are all HIPAA covered entities and will comply with all HIPAA regulations regarding data security. A data use agreement through the VA will be obtained to allow sharing of limited data with UCD and KPWHRI. All study files at each site will contain the minimum data necessary to accomplish the research activities at each site. Paper copies of records will be stored in locked files at the study team's work area at VA Puget Sound and will be accessible only to IRB-approved research staff. Electronic data access will be password protected and subject to the same security protections as other confidential patient data. Access will be limited to staff working on this study who require access to these files. Access to study data will be removed for study personnel when they are no longer part of the research team. All staff will be trained in appropriate security protections, computer passwords will be changed on a regular basis, and all staff will sign annual confidentiality agreements. Baseline surveys conducted at the VA will be done on the telephone, with data entry by the coordinator into VA RedCap database hosted on the VA server. Data necessary to contact individuals who consent to be in the study will be shared with UCD and KPWHRI investigators by email using Azure encryption, where the data will be entered into UCD RedCap. Online surveys administered by UCD during the course of the intervention at 3 and 6 months of follow-up will be hosted also using UCD Redcap.

7. *Data transfer*. Transfer of data between VA Puget Sound, UC Davis, and KPWHRI will take place using Azure, a protective technology used by Azure Information Protection. It uses encryption, identity, and authorization policies to help secure file attachments and email. After UCD staff safely open the email, UCD staff will enter the PII into UCD Redcap, a web application tailored for multisite research studies to build and manage online project management databases. The REDCap program in general has sophisticated customizable capabilities important for quality and security including flexible form creation, granular user privileging, password management, user authentication, auto logout, logging and audit trails, data export and de-identification, and protective security measures. Only a limited dataset will be transferred from VA to KPWHRI or UC Davis, based on the terms of the DUA, containing the minimum required information necessary to contact the participants for the purposes of carrying out the intervention or coordinating follow-up surveys (this will include name, email, telephone number, and address as well as a variable to designate study assignment – intervention vs. control).

8. *Communication with participants*. Electronic communications from the intervention team at KPWHRI with participants may contain references to smoking behavior change goals set by participants (e.g., a reminder to practice not smoking in your car for a day) but will not contain sensitive personal health information (e.g., HIV serostatus, medication information).

9. *Participant identities.* Participants' identities will not be shared with anyone other than relevant study staff who need this information to perform their study roles. Identifiable information will not be kept with other study data. Participants will be identified only by study ID number that will be sequentially generated and will not contain any HIPAA identifiers in part or in entirety. The crosswalk that links the study ID number to the identifier will be stored in on the secure VA Puget Sound HSR&D drive (i.e. J drive) in a restricted-access, project-specific folder, to which only IRB-approved research personnel will have access.
10. *Reporting.* To report study results, we will use only aggregated data or otherwise unidentifiable data.

QUALITATIVE SUPPLEMENT

Protected Health Information (PHI)

Data obtained from CDW to identify and recruit eligible patients for the qualitative interviews will include the following PHI: scrambled SSN, name, mailing address, phone number, DOB, and dates of service utilization. Recruitment of clinical stakeholders will involve collection of the following PHI: name, email address, and phone number. Aside from recruitment purposes, no identifying information will be necessary or applicable to the research. Therefore, although a master cross-walk list of enrolled interview participants will be maintained on a secure server, the qualitative data (digital recordings and transcripts) will not contain any participant identifiers. Digital recordings of qualitative interviews with participants and subsequent transcripts will contain only a unique study ID assigned to the participant. We will ensure that all interview participants understand that they will be assigned a unique study ID that will be used to label all study data such that data could not be linked to individuals. PHI will not be disclosed.

Data Security Plan

After giving verbal consent to participate in the qualitative interview, patient and clinical stakeholder participants will be assigned a unique, randomly-generated Study ID number. A single master list ("crosswalk") will contain subject names, phone numbers, and participants' unique Study ID.

Demographic information will be collected during the qualitative interview by Puget Sound VA staff and coded with a confidential Participant ID into a VA REDCap database, hosted by the VA behind the VA firewall. Data entry will be done by VA study staff granted access via a user specific login and password, and will be restricted to individuals who have demonstrated profieciency with the data system.

REDCap is a widely-used, secure web application for building and administering online surveys and databases. The REDCap application is managed and supported by the VA Information Resource Center (VIReC) and is installed and accessible through the VINCI to VA researchers only behind the VA firewall, which provides an exceptional level of data security. VA REDCap has sophisticated customizable capabilities important for quality and security including flexible form creation, granular user privileging, password management, user authentication, auto logout, logging and audit trails, data export and de-identification, and protective security measures. Data collection during the qualitative interviews will be first captured on paper forms and then entered into the VA REDCap by a study coordinator. This data will include the demographic questions as outlined in the Qualitative Interview Guide for participants who consent to participate.

All qualitative interviews with participants will be conducted and recorded using 1 of 2 VA-approved recording options: Microsoft Teams, which can save audio files directly onto the secure drive, or with VA-approved, encrypted digital recorders which will record interviews from a speaker phone in a private room. During the COVID-19 pandemic, study staff will use personal phones with the caller ID number blocked to recruit and conduct phone interviews from home, in alignment with guidance from ORD stating that personal phones can be used to conduct research. Interviews that are digitally recorded will be recorded with VA-approved, encrypted digital recorders and stored in a secure, locked location. As applicable due to COVID-19 practices, recordings will then be transported (with authorization to transport sensitive information) back to VA Puget Sound. Notably, all research staff conducting interviews will have an approved Authorization to Transport Sensitive Information. Recordings will be uploaded to a password-protected folder on a secure server. Digital recorders will be kept in a locked, secure location when not in use. Digital recorders will be sanitized when no longer needed for the study.

The following steps will be taken to ensure the privacy and confidentiality of participants in the Qualitative Supplement:

1. The unique Study ID will be the only participant identifier used during all qualitative interviews so that the digital recordings and subsequent transcripts will be confidential.
2. At the end of each interview, the interviewer will securely transfer the digitally recorded interview data to a secure, project-specific, password-protected folder on the VA Puget Sound Health Services Research & Development server on a drive specifically designed to house and protect research data (J drive). The digitally recorded interview will be accessed only via the password-protected J drive on the HSR&D server.
3. The master list containing the crosswalk data will be maintained on an Excel spreadsheet on a secure, password-protected VA Puget Sound Health Services Research & Development server on a drive specifically designed to house and protect research data (VA Puget Sound HSR&D J drive).
4. The master list will be stored in an Excel spreadsheet in a separate folder from study data (digital recordings and interview transcripts).
5. Only the approved research team will have access to the master list.
6. The master list containing crosswalk data will not at any time be linked to study data (digital recordings or interview transcripts).
7. The master list will be destroyed in accordance with VHA’s Records Control Schedule (RCS 10-1).

All research staff conducting interviews and/or accessing data will be approved for VA research and will complete all mandatory annual trainings in data security and human subjects protections and be educated in the use of all data security procedures necessary to ensure patient privacy and data security. All research staff conducting interviews will have an approved Authorization to Transport Sensitive Information.

16.0 Communication Plan

PRIMARY INTERVENTION STUDY

VA Puget Sound researchers will hold regular phone and/or Teams or other teleconference meetings with the intervention teams at UCD and KPWHRI. These meetings may include co-investigators from the West Haven VA and FHCRC. During these meetings, any changes to protocol, informed consent, HIPAA authorization, or initial and continuing IRB approvals will be announced. The intervention team will be alerted via during the teleconference of any serious adverse events or unanticipated problems. Issues requiring more urgent attention will be communicated promptly upon learning of them via email and phone with the entire study team. All current documents will be made available to the intervention teams via email.

QUALITATIVE SUPPLEMENT

VA Puget Sound researchers will hold regular phone and/or Microsoft Teams meetings, which may include co-investigators. During these meetings, any changes to protocol, informed consent, HIPAA authorization, or initial and continuing IRB approvals will be announced. The intervention team will be alerted via during the teleconference of any serious adverse events or unanticipated problems. Issues requiring more urgent attention will be communicated promptly upon learning of them via email and phone with the entire study team. All current documents will be made available to the intervention teams via email.

9.0 Information Security and Data Storage/Movement

PRIMARY INTERVENTION STUDY

The Puget Sound VA staff will first enter data coded with a confidential Participant ID into a VA REDCap database, hosted by the VA behind the VA firewall. VA REDCap is a free web application tailored for research studies to build and manage online surveys and databases. VA REDCap has sophisticated customizable capabilities important for quality and security including flexible form creation, granular user privileging, password management, user authentication, auto logout, logging and audit trails, data export and de-identification, and protective security measures. Data collection during the screening phone calls will be first captured on paper forms and then entered into VA REDCap by a study coordinator. This data will include the results of the screening phone call and the baseline survey for participants who consent to enroll.

Based on the terms of the DUA, staff at the VA Puget Sound email the limited PII to UCD staff using Azure. After opening the encrypted email, UCD staff will enter the PII into a UCD REDCap database. Data shared by staff at the VA Puget Sound will be limited to patient eligibility and minimum contact information necessary to contact the participants for the purposes of carrying out the intervention or coordinating follow-up surveys. The results of the baseline surveys will not be entered into this database.

Data entry by VA study staff will be done on VA computers to ensure its security. Users access VA REDCap via a user specific login and password. Access to the VA REDCap WISH project will be restricted to individuals who have demonstrated proficiency with the data system. The study staff at VA Puget sound will closely monitor: a) participant accrual in relation to goals and timeline; b) the randomization

process and group comparability on the balancing variables; c) key baseline characteristics of the sample, by group.

At the end of the intervention, NIH data collected by KPWHRI and UCD as approved by their IRBs will be sent to the VA Puget Sound for analyses. All data will be transferred within the guidelines of the terms outlined by the existing DUA. Data will be merged with VA data, cleaned and verified, then downloaded into appropriate analysis software housed by the PLG on the VA Center of Innovation for Veteran-Centered and Value-Driven Care (COIN) secure computer network servers and handled in accordance with the COIN's extensive data security policy. The study data is backed up daily and maintained by the COIN. One official copy of all study data and a master data dictionary will be maintained and updated regularly by the study data manager. A specific folder will be created by COIN IT staff located on the J Drive for storage of electronic data.

All study information is accessible only by IRB approved study staff on a need-to-know basis. Limited analytic datasets are shared between authorized study personnel via secure transmission and/or via a secure virtual private network employing industry-standard password protection and data encryption. Study information is not disclosed to any third party except as required by law. Only aggregate data will be used to report study results. Patient identifiers will be retained per IRB permissions.

The data will be retained on the VA Puget Sound Health Care System network server or OI&T managed archived back-up media. If a new RCS is published prior to the end of this study all files with identifiable data for this study will be deleted from the VA Puget Sound Health Care System (VAPSHCS) network server folder no later than six months prior to the closure of the study. Once identifiable data can be destroyed, only deidentified data will be retained thereafter on the VAPSHCS network server. Otherwise, all data will be retained until the RCS is published.

Deleted files are recoverable only by Office of Information and Technology (OI&T) network administrators from back-up tapes maintained by VAPSHCS OI&T. The VAPSHCS HSR&D network backup and retention policy limits retention of network backup tapes containing protected health information to no more than six months from the date that the data were deleted from the network server. After six months, monthly backup tapes are reused for disaster recovery or new monthly backup purposes. If the backup tape fails or is no longer in use for any reason, it will be destroyed by VAPSHCS OI&T staff, in compliance with VA policies for destruction of this
media type. Therefore, the identifiable data for this study will not be recoverable, consistent with IRB requirements.

QUALITATIVE SUPPLEMENT

The study is designed to specifically minimize risks to subjects. We will implement and strictly adhere to several security measures designed to protect patient confidentiality and ensure data security. Key aspects of these security measures include:

After giving verbal consent to participate in the qualitative interview, participants will be assigned a randomly-generated unique Study ID number. A single master list ("crosswalk") will contain subject names, phone numbers, and participants' unique Study ID.

We intend to store demographic information collected during the qualitative interview in a VA REDCap database coded with a confidential Participant ID and hosted by the VA behind the VA firewall. Data entry will be done by VA study staff granted access via a user specific login and password, and will be restricted to individuals who have demonstrated profieciency with the data system.

REDCap is a widely-used, secure web application for building and administering online surveys and databases and is managed and supported by the VA Information Resource Center (VIReC) as described above.

All qualitative interviews with participants will be conducted and recorded using 1 of 2 VA-approved recording options: Microsoft Teams, which can save audio files directly onto the secure drive, or with VA-approved, encrypted digital recorders which will record interviews from a speaker phone in a private room. During the COVID-19 pandemic, study staff will use personal phones with the caller ID number blocked to recruit and conduct phone interviews from home, in alignment with guidance from ORD stating that personal phones can be used to conduct research. Interviews that are digitally recorded will be recorded with VA-approved, encrypted digital recorders and stored in a secure, locked location. As applicable due to COVID-19 practices, recordings will then be transported (with authorization to transport sensitive information) back to VA Puget Sound. Notably, all research staff conducting interviews will have an approved Authorization to Transport Sensitive Information. Recordings will be uploaded to a password-protected folder on a secure server. Digital recorders will be kept in a locked, secure location when not in use. Digital recorders will be sanitized when no longer needed for the study.

The following steps will be taken to ensure the privacy and confidentiality of participants in the Qualitative Supplement:

1. The unique Study ID will be the only participant identifier used during all qualitative interviews so that the digital recordings and subsequent transcripts will be confidential.
2. At the end of each interview, the interviewer will securely transfer the digitally recorded interview data to a secure, project-specific, password-protected folder on the VA Puget Sound Health Services Research & Development server on a drive specifically designed to house and protect research data (J drive). The digitally recorded interview will be accessed only via the password-protected J drive on the HSR&D server.
3. The master list containing the crosswalk data will be maintained on an Excel spreadsheet on a secure, password-protected VA Puget Sound Health Services Research & Development server on a drive specifically designed to house and protect research data (VA Puget Sound HSR&D J drive).
4. The master list will be stored in an Excel spreadsheet in a separate folder from study data (digital recordings and interview transcripts).
5. Only the approved research team will have access to the master list.
6. The master list containing crosswalk data will not at any time be linked to study data (digital recordings or interview transcripts).

7. The master list will be destroyed in accordance with VHA's Records Control Schedule (RCS 10-1).

All research staff conducting interviews and/or accessing data will be approved for VA research and will complete all mandatory annual trainings in data security and human subjects protections and be educated in the use of all data security procedures necessary to ensure patient privacy and data security. All research staff conducting interviews will have an approved Authorization to Transport Sensitive Information

As a result of these measures, we do not expect any invasion of privacy or breach of confidentiality for any subject included in this study and believe all risks involved with the study are minimal.

All research records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration (NARA) and are published in VHA's Records Control Schedule (RCS 10-1). (VHA Handbook 1200.05). Analytic datasets will be stored consistent with these policies.

11.0 References

Bibliography of cited literature

4.4 STATISTICAL DESIGN AND POWER

Sample Size and Power:

Original Power and Sample Size Calculation

This study was originally powered on the primary outcome of 7-day point prevalence abstinence at 6 months, assuming a base rate of 0.10 in the control arm. Based on this assumption, we proposed recruiting 250 people per arm for a total sample size of 500 individuals. This sample size would give us 80% power to detect an absolute difference of 0.07 in the PPA rates between arms with no attrition, and an absolute difference of 0.10 in the PPA rates with 20% attrition in each arm. For the binary secondary outcome of any quit attempt during 6 month follow-up, we assumed a base quit attempt rate of 20% to 25% in the control arm, which would give us 80% power to detect quit attempt rates of 12% and 13% in the intervention arm, respectively.

Revised Power Analysis

In consultation with the DSMB, it was decided to use available data from the control arm at baseline and 6 months to inform a revised power analysis based on the most recent enrollment projections. Based on those projections, we expect to recruit a total of 113 people per arm for a total sample size of 226. Data from the intervention arm were not used in this revised power analysis to avoid interim assessment of intervention effects.

Summary of interim follow-up data in control arm

We had baseline data on 50 individuals in the control arm, 26 of whom had follow-up data at 6 months on quit attempts and 25 of whom had 6 month follow-up data on 7-day PPA. The observed 7 day point smoking abstinence rate among responders was 0.05 (1/25). Under the missing = smoker assumption, the 7 day abstinence rate would be 0.02 (1/50). The observed quit attempt rate was 0.54 (14/26). The average number of cigarettes smoked per day was 12.4 with a standard deviation of 9.8, compared to an average of 15.9 cigarettes smoked per day at baseline with a standard deviation of 9.1.

Revised Power Analysis

Primary Outcome - 7 day point smoking abstinence at 6 months

In the full sample where missing data are imputed under the missing = smoker assumption, we estimate having 80% power to detect an intervention effect that results in an abstinence rate of 0.16 in the treatment arm if the control arm abstinence rate is 0.05, and 80% power to detect an intervention effect that results in an abstinence rate of 0.11in the treatment arm if the control arm abstinence rate is 0.02. In the responder-only sample assuming a retention rate of 60%, we estimate having 80% power to detect an intervention effect that results in an abstinence rate of 0.21 in the treatment arm if the control arm abstinence rate is 0.05, and 80% power to detect an intervention effect that results in an abstinence rate of 0.15 in the treatment arm if the control arm abstinence rate is 0.02.

Secondary Outcome - Quit Attempt within 6 months

Assuming a quit attempt rate of 0.54 in the control arm and a retention rate of 0.60, we estimate having 80% power to detect an intervention effect that results in a quit attempt rate of 0.31.

Secondary Outcome - Cigarettes Smoked per Day

Assuming a standard deviation of 9 cigarettes smoked per day and a retention rate of 0.60, we estimate having 80% power to detect an absolute difference in the mean number of cigarettes smoked per day of 4.36 cigarettes. Assuming that the mean number of cigarettes smoked per day in the control arm is 12, this translates to an average of 7.64 cigarettes smoked per day in the intervention arm.

Summary Tables

Table 1: Intervention Effects Detectable with 80% Power

No. Enrolled	Retention Rate	Cessation Rate (Control Arm)	Cessation Rate (Intervention Arm)	Risk Difference
200	0.6	0.02	0.17	0.15
200	0.7	0.02	0.15	0.13
200	0.8	0.02	0.14	0.12
200	1.0	0.02	0.12	0.10
200	0.6	0.05	0.22	0.17
200	0.7	0.05	0.21	0.16
200	0.8	0.05	0.19	0.14
200	1.0	0.05	0.17	0.12
200	0.6	0.10	0.30	0.20
200	0.7	0.10	0.29	0.19
200	0.8	0.10	0.27	0.17
200	1.0	0.10	0.25	0.15
226	0.6	0.02	0.15	0.13
226	0.7	0.02	0.14	0.12
226	0.8	0.02	0.13	0.11
226	1.0	0.02	0.11	0.09
226	0.6	0.05	0.21	0.16
226	0.7	0.05	0.19	0.14
226	0.8	0.05	0.18	0.13
226	1.0	0.05	0.16	0.11
226	0.6	0.10	0.29	0.19
226	0.7	0.10	0.27	0.17
226	0.8	0.10	0.26	0.16
226	1.0	0.10	0.24	0.14
250	0.6	0.02	0.14	0.12
250	0.7	0.02	0.13	0.11
250	0.8	0.02	0.12	0.10
250	1.0	0.02	0.11	0.09
250	0.6	0.05	0.20	0.15
250	0.7	0.05	0.19	0.14
250	0.8	0.05	0.17	0.12
250	1.0	0.05	0.16	0.11
250	0.6	0.10	0.28	0.18
250	0.7	0.10	0.26	0.16
250	0.8	0.10	0.25	0.15
250	1.0	0.10	0.23	0.13

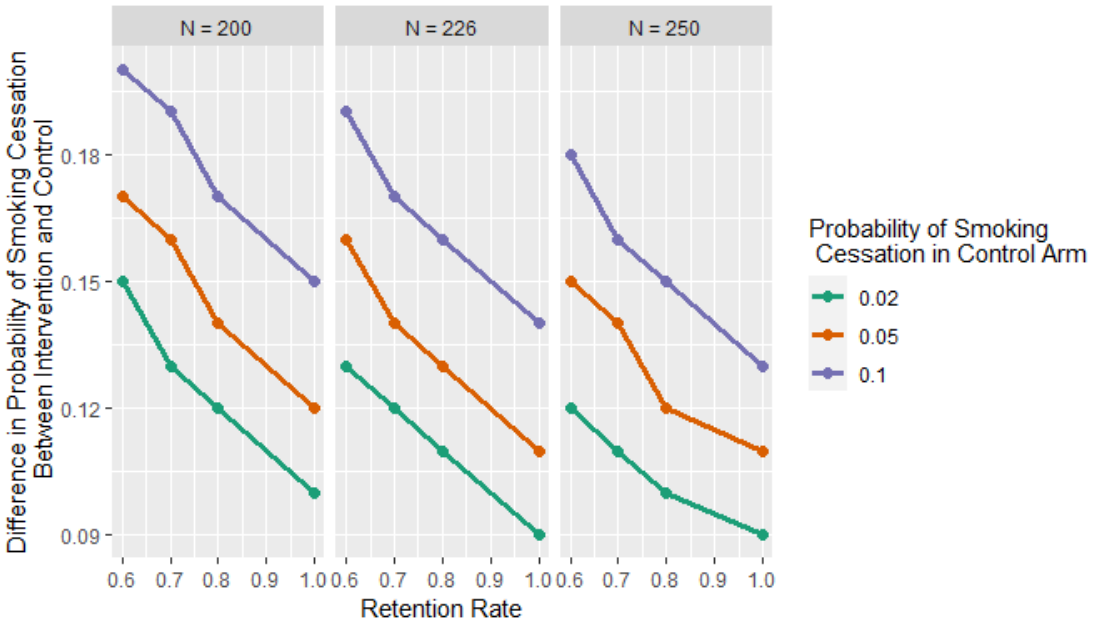


Figure 1. The effect sizes detectable with 80% power, expressed in terms of the difference in probability of smoking cessation between intervention and control arm, plotted against retention rates for different values of total enrollment (panels) and smoking cessation rates in the control arm (colored lines).

Data Analyses.

All analyses will use an intent-to-treat (ITT) approach. Individuals will be analyzed by randomization group regardless of their utilization of assigned treatments. All analyses will be performed using the R statistical computing environment (https://www.R-project.org/). Robust sandwich-style standard errors will be used to account for potential violations of the model-based variance structures for linear and Poisson regressions. Confidence intervals for parameter estimates will be based on a confidence level of 95%. Hypothesis tests will be double-sided and based on a significance level of 0.05.

Aim 1. Compare the effectiveness of experimental and control arms by comparing biochemically verified 7-day PPA at 6 months, and patient reported 24-hour intentional quit attempts, prolonged abstinence, 7-day PPA, 30-day PAA, cigarettes smoked per day, at 3, 6 and 12 months post-randomization.

Analyses of Primary Smoking-Related Outcomes. We will first use chi-square analyses to compare the percentages in the control and intervention groups who are abstinent by the confirmed 7-day PPA intent-to-treat measure. We will then repeat these analyses using logistic regression to control for the four baseline variables which we used in the block randomization (recruitment site, baseline intention to quit within 30 days, number of cigarettes smoked per day <10, sex), since failure to do so can result in biased estimates of the treatment odds ratio. In addition, we will fit a second adjusted model which adjusts for these stratification variables. In all of these analyses, anyone with missing data on smoking status at follow-up will be assumed to be smoking. Following the Russel Standard,174 unless deceased, respondents who are missing PPA outcome data will be classified as smokers in the primary analysis. If missingness is non-

differential between treatment arms, classifying non-responders as smokers will tend to produce a conservative effect estimate biased towards the null hypothesis of no difference between intervention groups. In the Dropout Analyses section, we describe alternative approaches we will use to examine the sensitivity of our estimates to this assumption. For the outcome of 24-hour quit attempts post randomization, we will analyze this outcome both as a binary measure (none vs. 1+ attempts) and as a count type variable. For the binary measure, we will do unadjusted chi-square tests and adjusted analyses using the same two logistic models described above with the addition to the models of baseline number of quit attempts in the prior year. For the count version of this measure, we will compare mean number of quit attempts in the groups using t-tests/Wilcoxon tests (unadjusted analyses). For the adjusted analysis we will fit the same two models using either ordinary least-squares regression or Poisson regression (choice will depend on the shape of the distribution for the number of attempts). When smoking status is unknown or the quit attempt question is not answered, we will assume that the person made no quit attempts.

Analyses of Secondary Smoking-Related Outcomes. Analyses of number of cigarettes smoked per day, self-report PPA, and floating prolonged abstinence outcomes will be done in a similar manner to that used for the primary smoking outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). We will use regression modeling to examine the effect of the intervention over the entire course of follow-up, using generalized estimating equations (GEE) to account for the within-subject correlation over time. We will quantify a potential non-constant intervention effect over time using interaction terms. If there is sufficient evidence of a non-constant intervention effect, we will use month 6 follow-up as the primary time point of interest. Otherwise we will use the GEE regression model to estimate the effect of intervention using the entirety of the follow-up data.

Aim 2. Describe the reach and implementation of the HIV-specific comprehensive intervention.

Descriptive and bivariate analyses will be used to characterize absolute number, proportion and representativeness (in terms of current readiness to quit, smoking history and demographic characteristics, antiretroviral use, comorbidities such as non-AIDS defining cancers, and HIV-related co-infections) of smokers living with HIV who are willing versus unwilling to enroll in the program, who do or do not enroll in standard VA cessation services, and who use or do not use NRT or other cessation medications during the study period. comparisons will be made using t-tests or Wilcoxon-Mann-Whitney non-parametric tests for continuous/ ordinal variables and chi-square for binary outcomes. In addition, we will use multiple regression models to explore how predictive these factors are in combination of willingness to enroll, utilization of VA standard cessation services, and use of cessation medications.

Aim 3. Compare cognitive-behavioral change process variables based on the Information-Motivation- Behavioral Skills Model for Smoking Cessation (i.e., HIV specific smoking-related knowledge, self-efficacy for quitting or reducing smoking, motivation to quit, and cessation-related behavioral skills including cessation medication use/ adherence) between the experimental and control arms at 3, 6 and12 month follow-up.

Analyses of intermediate change process outcomes will be done in a similar manner to that used for the smoking - related outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). For outcomes such as self-efficacy, adjusted models will always include the baseline measure of the outcome under analysis (note, we cannot do this for cessation since 100% are smoking at baseline). We expect to use least squares regression to analyze HIV-specific smoking knowledge, motivation to quit, self-efficacy for quitting and reducing smoking, and cessation-related behavioral skills, (possibly after a transformation to account for possible left or right skewness). We will use a similar approach to evaluate NRT and/or other cessation medication use and adherence. We will also test if the effect of the intervention is constant across the three follow-ups using GEE.

Aim 4. Compare CD4 T-cell count and VACS Index of mortality risk between arms at 6 and 12 months.

Analyses of secondary HIV-related outcomes will be done in a similar manner to that used for the primary and other secondary outcomes: unadjusted (chi-square for binary, t-test/Wilcoxon for means) then reduced and fully adjusted models (logistic for binary, least-squares or Poisson regression for means). For outcomes such as CD4 count and VACS Index, adjusted models will always include the baseline measure of the outcome under analysis. The VACS Index is a validated, generalizable risk index for predicting all-cause mortality that uses routine clinical laboratory data141,178. We will compute the VACS Index 2.0 version based on the following variables obtained from the VACS database that are also in the original 1.0 version: age, CD4, HIV-1 RNA, hemoglobin, alanine and aspartate transaminases, platelets, creatinine and hepatitis C virus serostatus, along with the new variables of albumin, white blood count, and body mass index in the 2.0 version that improve discrimination for mortality125. Each 5-point increase in VACS Index 2.0 score reflects an approximate 1.3-fold increase in mortality, and preliminary analysis suggests scores are higher among current smokers compared to former or never smokers125. We will test the hypothesis that participants randomized to the intervention arm will experience a greater reduction in VACS Index 2.0 scores over 6-12 months compared to the control arm,
potentially due to smoking reduction, smoking cessation and/or other wellness focused changes in behavior that may be reflected in the biomarkers of the Index.

Dropout Analyses. The Russel Standard of counting non-responders as continued smokers is appealing as a way to ensure uniformity in the handling of missing data in smoking cessation studies. However, it is difficult to justify statistically, and its impact on the scientific conclusions of a study must be considered. To this end, we propose to perform a thorough investigation of the impact of the “missing = smoker” assumption by considering several different statistical approaches to handling non-response. Estimates of the effect of the intervention under these alternative specifications of the missing data mechanism will be compared to the estimates obtained using the “missing = smoker” assumption to see how sensitive our results are to this assumption.

The “missing = smoker” assumption is a form of deterministic imputation that can affect p-values and confidence intervals by artificially reducing the variance of the data179. To address this shortcoming, we will repeat the analyses of our primary outcomes using less deterministic imputation procedures. We will examine patterns of missingness in the two intervention arms to determine to what degree non-response differs between the two arms and to determine relevant baseline characteristics that are related to non-response. We expect variables such as readiness to quit and level of nicotine dependence to be important factors in these models, but

other baseline variables may be included as well. We will then use these baseline measures to construct imputation models for the missing responses. Multiple imputation procedures will be used to correctly account for the uncertainty in imputed values, resulting in valid p-values and confidence intervals. First, we will refit the regression models described in the previous aims using the imputed data to obtain estimates of the effect of the intervention consistent with a Missing at Random non-response model. Then, we will conduct sensitivity analyses under the assumption of non-ignorable non-response, also referred to as Missing Not at Random180. As noted in Hedeker179, the Russel Standard of counting all non-responders as continued smokers is itself a form of non-ignorable non-response, in that it assumes a direct relationship between missing status and the unobserved outcome. Since assumptions regarding nonignorable non-response cannot be checked using the observed data, it is important to consider alternative specifications for these types of models. To achieve this, we will use a 2-step GEE imputation method180. This method provides a flexible and transparent approach to handling non-ignorable missingness that improves upon the Russel Standard both by accounting for the uncertainty of the imputation method when calculating standard errors as well as by incorporating available covariate information.

Consent and Authorization to participate as a Research Subject in:

The WISH Study

SUMMARY OF STUDY: The purpose of this study is to help people living with certain health conditions take better care of their health. You do not have to be ready to make a behavior change to participate.

As a study participant, you may receive a phone-based counseling program and text messages. You will also be encouraged to make one or more healthy lifestyle changes and to use other treatments available at VA Puget Sound Health Care System. Study participation will be for about 6 months.

This study will allow us to examine how well the WISH counseling program works compared to standard care treatment.

We are inviting you to be in a research study. The purpose of this Consent Form is to give you the information you will need to help you decide whether to be in the study. Please read this form carefully.

You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear.

Principal Investigator:
<removed>

Study Line:
<removed>

Study Title:
Wellness **I**ntervention for **S**mokers' **H**ealth (WISH)

Your participation in this study is entirely voluntary. Please take as much time as you need to discuss the study with your doctors, family, and friends. The decision to participate or not is yours. If you choose to participate, you have the right to withdraw from the study at any time.

This study is sponsored by the National Cancer Institute of the National Institutes of Health.

1. Who can I contact with questions while I am in this study?

During business hours (8:00 a.m. – 4:30 p.m.), please call the Research Coordinator or Principal Investigator at <removed>. After business hours (nights and weekends), please call <removed> and ask the operator to page the on-call pulmonary doctor.

The study researcher(s) listed above must be contacted immediately if:

- You think you may have been harmed or injured as a direct result of this research.
- You have any questions regarding your medical care issues specifically related to the study.

You may also contact the Institutional Review Board (IRB) at <removed> if you:

- Would like to speak with a neutral party who is not involved with this study.
- Have questions, concerns, or complaints about the research.
- Would like to verify the validity of the study.
- Have questions about your rights as a research subject.

2. What is the purpose of this research study?

The purpose of this study is to help people living with certain chronic health conditions take better care of their health by making healthy lifestyle changes. We are enrolling people who currently smoke cigarettes and who receive care in the VA.

Two other research sites (University of California and Kaiser Permanente Washington Health Research Institute) will also be participating in this study. In the VA, we will enroll up to 520 subjects to participate.

We will be comparing a study treatment to usual care treatment in helping people make important behavior changes that can improve their health. This includes, but may not be limited to, quitting smoking. However, you do not have to want to quit smoking or to make other behavior changes in order to be in this study. We only ask that you consider using the services and support we provide.

If you are interested in being in this study, we will need up to 6 months of your time, but we may collect information from your medical record for up to one year after your enrollment. All study contact will be done by phone, text message, or online.

You should not participate in any other behavioral intervention studies over the next 6 months without consulting the Principal Investigator or research staff. Participation in other studies could undermine the results of this study.

3. What will I be asked to do in this research study?

<u>Counseling</u> (phone calls and texts)

You will be randomly assigned to one of two groups (Group A or B). This assignment is done by a computer and is based on chance (like the flip of a coin).

People in both groups will be offered phone counseling (up to 5-6 calls, depending on the group) and a series of supportive text messages. Phone sessions will be recorded to ensure that the counselors are covering all topics that need to be covered in the sessions. You may refuse to have your sessions recorded and still be in the study. All phone counseling will be provided by trained staff outside of the VA. Each group will be contacted by counselors from different sources, as follows:

- **Group A.** People in Group A will receive calls from counselors at the National VA Quitline. In addition, Group A may sign up for texts, but this is optional. If you are in Group A and opt to receive texts, you will receive 3-5 texts a day for 6-8 weeks.
- **Group B.** People in Group B will receive calls from counselors at the Kaiser Permanente Washington Health Research Institute, one of the study sites participating in this research study. In addition, Group B will receive about 13 texts over a 6-week period.

We will also ask you questions about your medical history, health risk behaviors (such as smoking, alcohol use, or substance use), treatment adherence, physical activity, the types of social support you receive from others, and your mood.

The following table details each study activity and about how long it will take. Your active participation in this study will last about 6 months, but we may collect information from your medical record up to one year after your enrollment.

Study Activity	Estimated Duration
Phone screening & verbal assent	30 minutes
Baseline phone survey	30 minutes
Follow-up online survey (3 months)	30 minutes
Follow-up online survey (6 months)	30 minutes
Counseling sessions: • Group A (5 calls total) • Group B (6 calls weekly)	 20 minutes each 30 minutes each
Text messages: • Group A • Group B	Optional program. If signed up, you can receive 3-5 texts day for 6-8 weeks.
If selected: Saliva test via VA video connect at home	30 minutes

We may also collect information from your medical records for up to one year after your enrollment. This would include records such as laboratory results, other markers of disease progression, or information about changes in your health status that may occur as a result of being in this study. This information will be kept confidential as provided by law, as described in Section 7 below.

If you report that you have quit smoking at your 6-month follow-up and do not use other nicotine products, we may randomly choose you to complete a saliva test to confirm that you have quit. If you are chosen, we will mail you an easy-to-use kit to collect your saliva.

Once you receive the kit, we will have you download a mobile app called VA Video Connect. To download the app, you will need to have a computer, tablet, or smart phone. Through Video Connect, you will be able to virtually connect with a member of the study staff. This will enable you to perform the saliva test while in a virtual medical room.

The saliva test includes spitting into a tube and then sticking a test strip into the tube. Since the results take 15-30 minutes, the study staff member that you are connected with will ask you a few questions about what it was like to participate in the study.

The study staff member will then take a screenshot of the test strip only. At the end of the call, you can throw the test strip away.

4. What are some risks of joining this research study?

The study procedures may involve risks that are currently unknown. We may need to contact you if we learn of a new study risk, even if you have completed the study. If any of the risks included in this Consent Form become significantly updated during this study, we may ask you to sign an updated Consent Form to document that this new information has been explained to you. You will have the right to decide either to continue with the research study or to withdraw.

Below are study-related risks that are known at this time:

Phone calls. You may feel uncomfortable answering some study questions or discussing some health topics with your counselor. If so, you do not have to answer these questions or discuss these topics.

Audio-recording. We will not place your name or any identifying information on the audio-recording. However, because your voiceprint is considered a "personal identifier" according to the patient privacy rules, the research team will ensure the security of these recordings. The recording will be erased from the recorder after it has been moved electronically to a secure VA server. Our methods of securing your privacy and confidentiality are described in Section 7.

Text messaging. Text messages will come from the research team at Kaiser and VA Puget Sound. These messages from KP staff will be sent using a web-based application called StudyPages and messages from VA staff will be sent from a secure VA issued phone. We cannot guarantee the security of electronic communications. Texts will not include sensitive health information but will be reminders about appointments and general messages to check in on your progress with your goals. In addition, there is the possibility of increased cost related to the text messaging for purposes of this study.

VA Video Connect. Your video session will not be recorded or shared outside the VA study staff. All Video Connect sessions are completed behind the secure VA firewall and are encrypted and secure, but we cannot guarantee the privacy on your home computer. Take precautions to check that you are running the most current version of your software and any security program.

Withdrawal. If you change one or more of your health behaviors, you could experience side effects. For example, if you stop smoking, you may experience symptoms of nicotine withdrawal, including cravings to smoke, irritability, mood changes, trouble sleeping, constipation, and difficulty concentrating. If you choose to use a stop-smoking medication, you might experience medication-specific side effects. Please discuss these with your doctor before starting any new medication.

Internet. Any activity on the internet involves risk and, in using your own computer, you should take the normal precautions of ensuring that your system is running the most current version of your browsing software, that you have up-to-date virus protection, and that you implement a software or hardware firewall to protect your computer and yourself. If you choose to use a public computer to access this resource (such as a library computer), know that your information is only as safe as that computer's safety features. Any website can be hacked. By ensuring your computer has up-to-date security measures, you can reduce the risk to yourself, but risk cannot be totally eliminated.

Confidentiality. It is possible that someone could learn you are in a study involving people living with certain chronic health conditions. To minimize this risk, we will not include sensitive health information in any electronic communications we send you (such as the texts) and we ask that you not send sensitive information to us by text or email because we cannot guarantee the security of electronic communications. If you are randomized to have a Video Connect session, the video session will be conducted behind the VA firewall. We will also take other steps to protect your privacy (see the Section 7 below).

5. What are some benefits of joining this research study?

There may be no direct benefit to you by participating in this study. However, you may learn ways to better manage your health or make other positive health changes, including reducing or quitting smoking.

6. Are there other ways I could receive these benefits?

This study is voluntary and for research purposes only. The alternative to the study is to not take part in it.

We encourage you to talk with your VA doctor about other treatments available through the VA. This includes medications to help you stop smoking. Your use of any of these services is voluntary.

7. Who will see my information and where will it be stored?

Your research information will be kept confidential. However, some data will be shared, communicated, or stored during or after this research study.

The access to your records, including your medical records, could be either for study-related purposes or to make sure your study record meets all legal, compliance, and administrative requirements. The reviewers will protect your privacy.

Certificate of Confidentiality

We have a Certificate of Confidentiality from the National Institutes of Health. The researchers will use the Certificate to resist any demands, even by a court of law, for information that would identify you. You may still share information about yourself or your part in this research as you see fit.

The Certificate of Confidentiality does not protect us from:

- Disclosing information to the National Cancer Institute, the Sponsor of the study.
- Disclosing information to state or federal public health authorities to whom certain contagious diseases (tuberculosis, HIV, anthrax, syphilis) are reported (if we observe such diseases in any subjects).
- Disclosing information to law enforcement authorities if we get any information that suggests the occurrence of child abuse, elder abuse, or your intent to immediately and substantially harm yourself or others.

- Giving the VA Puget Sound office that manages payments to subjects your name, social security number, address, and the name of this study.
- Giving your name to state, federal, and institutional offices involved in auditing or compliance of research, risk management, patient safety, and financial controls.

We will only share the minimum necessary information with research staff at the University of California or Kaiser Permanente Washington Health Research Institute so that they can contact you. Staff at these sites will help conduct the online follow-up surveys, counseling phone calls, and send some text messages.

To make sure no one other than study personnel can match you to your data, we will use a unique study code instead of identifying information, such as your name or social security number, to code (label) your study data. This study code can be linked to your contact information. The link will be stored separately from the data on a secure server at VA Puget Sound. Access to your study records will be password protected and only staff who need to access this in order to perform their jobs will be given access. Non-electronic study records will be kept in locked file cabinets. All electronic transfers of data will be password protected and encrypted.

Audio-recording. All recordings will be stored on a secure server at Kaiser Permanente and will be erased after data is analyzed for the study. Digital recorders containing audio-files that have not yet been uploaded onto the server will be stored in locked file cabinets inside of locked offices until the audio-files are removed from the recorders.

Video Connect (if applicable). We will not record the video session. The purpose of the video is to confirm that it is your saliva and to be able to take a screenshot of the test strip results. We will not take any other screenshots. We will not share the results with anyone outside the research study staff.

Once this study is completed, we will not use your data, including any recordings (or the study code linking it to you) for any additional research. We will keep your data and code in a secure database in accordance with the VA records retention policy (which will be a minimum of 6 years after the study has been completed).

In the future, researchers may write about the information collected from this research study. Any future publications or articles will not include any identifying information about you without your approval in writing. Neither you nor your family will gain financially from discoveries made in the future using the information you provide.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

8. What are some other things to think about before I decide to join this research study?

The VA requires some Veterans to pay co-payments for medical care and services. You will still have to pay these co-payments as long as they are not related to this research study.

If participants contact the study team upon receiving initial mailing, they are eligible to receive a one time payment of $20.

You will receive $30 compensation for each study survey you complete. If you complete all three surveys, you will receive an additional $10 bonus (up to $100 total). You should receive payment 8-12 weeks after completion of each survey.

If randomly selected for the saliva test at the end of the study, participants will receive an additional $20 payment upon completion.

To comply with Internal Revenue Service (IRS) guidelines, we will collect your social security number. You may receive an IRS Form 1099.

9. What will happen if I decide I don't want to be in this research study later?

You do not have to take part in this study. If you are in this study, you can withdraw at any time. If you decide not to participate or to withdraw, no action will be taken against you; for instance, you will not lose your VA benefits.

If you decide to withdraw from the study, no new information will be collected from you. Information already collected up to that point will continue to be used for the study.

The research team may withdraw you from this study without your consent if the study is stopped or there is a medical reason to remove you.

You can also withdraw from the study intervention and continue to complete study surveys or data collection from medical records. If you decide to withdraw from all or parts of the study, you may receive a letter and follow up calls from the study team to confirm what parts of the study you want to withdraw from.

10. What will happen if I am hurt in this research study?

If you are injured as a result of participation in a VA-approved research study, the VA will provide you with the necessary medical treatment. You will not be charged for this treatment. Veterans who are injured because of being in this study may receive payment under Title 38, United States Code, Section 1151. Veterans or non-Veterans who are injured may receive payment under the Federal Tort Claims Act.

You do not waive any legal rights by signing this Consent Form.

11. Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private health information. Federal laws, state laws, and the federal medical law known as the HIPAA Privacy Rule also protect your privacy. By signing this Consent Form, you provide your permission, called your "authorization," for the use and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this Consent Form. They may also collect other information including include information applicable to the study; for example, your name, address, date of birth, and information from your medical record such as HIV status; drug, alcohol, or sexually transmitted disease treatment; or mental health treatment.
The following list of people or groups may know that you are in this study. They may have access to your research records, which may include your medical records:

- Research team members
- National Cancer Institute, Sponsor
- Seattle Institute for Biomedical and Clinical Research (the nonprofit institute that works with VA Puget Sound to conduct research) will be provided with your full name, address, phone number, and social security number in order to authorize payment for your participation in this study
- Other federal agencies including, but not limited to, the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP), the VA Office of Research Oversight (ORO), the VA Office of the Inspector General (OIG), and the Government Accountability Office (GAO)
- The VA committees that oversee research
- University of California and Kaiser Permanente Washington Health Research Institute, participating research sites

Identifiable health information will be disclosed (given) to the following individuals or groups

- National Institutes of Health and/or the Sponsor's legal Agent when applicable. Health information in your medical record shared with the study funder (sponsor) or their agent is limited to information directly related to this research study.
- University of California at Davis
- Kaiser Permanente Washington Health Research Institute

Type of identifiable health information that will be disclosed

University of California at Davis (UC Davis):

- Data collected from you to be able to contact you for the WISH counseling program: First and last name, electronic mail address, a phone number, and a mailing address.
- Data collected through the UC Davis application: Survey responses and results.
- Passive information collected when using a computer or phone to answer surveys may include type of device, device unique identifier, resolution of device, operating system and version, browser type and version, carrier information, geographical location data, crash reports, cookies, click tracking, and Internet Protocol (IP) address.

Kaiser Permanente Washington Health Research Institute:

- Data collected from you to be able to contact you for the WISH counseling program: First and last name, electronic mail address, a phone number, and a mailing address.
- Data collected through the Kaiser application: Phone calls and text messaging with the intervention team to improve health.
- Passive Information collected when using a phone may include type of device, device unique identifier, resolution of device, operating system and version, browser type and version, carrier information, geographical location data, crash reports, cookies, click tracking, and Internet Protocol (IP) address.

Your health information disclosed pursuant to this authorization may no longer be protected by federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization in writing at any time. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, Dr. Crothers and her research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment, or enrollment/eligibility for benefits cannot be conditioned on your signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

12. What am I agreeing to by signing this form?

I have read or have had read to me all of the above. The study has been explained to me, including a description of what the study is about and how and why it is being done. All of my questions have been answered. I have been told of the risks and/or discomforts I may encounter in the study, of the possible benefits of the study, and of the other choices of treatment that are available to me.

My rights as a research subject have been explained to me and I voluntarily consent to participate in this study. I will receive a copy of this Consent Form.

I agree to participate in this research study as described in this document.

_____ _____

Subject Signature Date

_____

Print Name of Subject