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Design and Methods of a Randomized Trial Testing the Novel Wellness Intervention for Smokers Living with HIV (WISH)

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Abstract

Smoking rates are disproportionately high among people living with HIV. Smokers living with HIV (SLWH) are also largely unaware of the HIV-specific deleterious effects of smoking and often lack motivation and confidence in their ability to quit tobacco. To address these issues, we

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

developed the Wellness Intervention for Smokers Living with HIV (WISH). WISH is grounded in the Information-Motivation-Behavioral Skills (IMB) Model and is designed for *all* SLWH, regardless of their initial motivation to quit. It follows evidence-based, best practice guidelines for nicotine dependence treatment, but is innovative in its use of a comprehensive wellness approach that addresses smoking within the context of HIV self-management including treatment adherence and engagement, stress management, substance use, and other personally relevant health behavior goals. The described randomized trial will enroll SLWH who are receiving care at Veterans Affairs (VA) medical centers and compare WISH's impact on smoking behavior to standard care services offered through the National VA Quitline and SmokefreeVET texting program. It will also assess intervention impact on markers of immune status and mortality risk. If effective, WISH could be disseminated to Veterans nationwide and could serve as a model for designing quitline interventions for other smokers who are ambivalent about quitting. The current paper outlines the rationale and methodology of the WISH trial, one of a series of studies recently funded by the National Cancer Institute to advance understanding of how to better promote smoking cessation among SLWH.

Keywords

smoking cessation; tobacco; counseling; behavior; text messaging; HIV; Veterans

1. Introduction

Smoking rates among people living with HIV (PLWH) are two to three times higher than in the general population, [1] and PLWH now lose more life-years to tobacco-related diseases than to their HIV infection.[2] Smoking among PLWH is also associated with increased risk of AIDS-defining illnesses such as bacterial pneumonia, lung cancer and other malignancies,[3-13] and PLWH who smoke have a two-fold greater mortality compared to those who do not.[3-13] Finally, smokers living with HIV (SLWH) may have poorer viral and immunologic responses to antiretroviral therapy (ART) and higher risk of developing AIDS.[3, 14-16] Smoking cessation can reduce morbidity and mortality and improve quality of life among SLWH.[17] As such, quitting smoking is critical in this high-risk, medically-vulnerable population.

National treatment guidelines for smoking cessation recommend that PLWH be offered evidence-based treatment for nicotine dependence.[17, 18] Best-practice treatment combines advice to quit, skills-based training (counseling and self-help) and pharmacotherapy (e.g., NRT, varenicline, bupropion) and can double quit rates for tobacco among smokers ready to quit.[19] However, this best-practice treatment has two significant limitations with regard to SLWH. First, comprehensive literature reviews have shown there are insufficient data to conclude that standard evidence-based, best-practice treatment is efficacious among SLWH.[20-22] To date, only 8 randomized efficacy trials have been published, each testing in-person or phone counseling + NRT[23-26], varenicline[27, 28], or an online intervention + NRT.[29] While significant abstinence effects were observed at 3-6 months in 5 studies, [23, 26-28, 30] long-term efficacy data are generally lacking. More research is clearly needed, particularly testing interventions tailored to the unique needs of SLWH. Second,

best-practice treatments are designed for smokers who are ready to commit to quitting, which is only a small proportion of smokers. Most persons who smoke (~70%) want to quit someday, but are not yet ready to commit to quitting; [31] they are ambivalent about quitting. This is also true of SLWH; research shows high rates of ambivalence in this population, despite a desire to quit someday.[1] Interventions that address this ambivalence and can engage and motivate SLWH to commit to quitting and then support their quit attempts by connecting them with evidence-based treatment could help. But to date, such interventions are generally not available, and we have found no published research demonstrating effective, evidence-based interventions for ambivalent SLWH.

This paper describes the rationale, design, and methods of the WISH trial, one of seven studies recently funded by the National Cancer Institute to develop and test augmentations to best-practice, evidence-based treatments for SLWH.[32] This trial will compare the effectiveness and reach of the Wellness Intervention for Smokers' living with HIV (WISH) against standard care services available to all Veterans who smoke. Unlike most standard care tobacco quitlines which target smokers ready to quit in the next month (i.e., preparation or action stages of change), WISH is designed for *all* people who smoke, regardless of their readiness to quit smoking in the near term, and it uses a comprehensive wellness approach to engage and motivate Veterans to make healthy lifestyle changes, including quitting smoking. If WISH is found to be effective, it could be disseminated nationally and serve as a model for other tobacco quitline programs.

2. Methods

2.1 Collaborating Sites and Oversight

The WISH trial is a collaboration between researchers at the Kaiser Permanente Washington Health Research Institute (KPWHRI), University of California at Davis (UCD), VA Puget Sound Health Care System (VA), University of Washington (UW), and Fred Hutchinson Cancer Research Center. The WISH intervention was initially developed by researchers at KPWHRI [33] and adapted for use with Veterans in this study. Study participants will be recruited and enrolled by staff at VA. Survey assessments will be conducted by UCD. The experimental intervention will be delivered by KPWHRI counselors and standard care, control intervention will be provided by staff at the Fred Hutchinson Cancer Research Center who provide contracted VA Tobacco Quitline services for Veterans nationally. Treatment fidelity monitoring will be conducted at KPWHRI. Finally, outcome data analyses will be conducted by the VA.

The WISH trial is funded by the National Cancer Institute (NCI) and is registered with ClinicalTrials.gov (NCT04505371). All research activities were reviewed and approved by the VA and UCD Institutional Review Boards. Human subjects' oversight at KPWHRI was ceded to UCD. The project is also overseen by a Data and Safety Monitoring Board (DSMB).

At the time this protocol was drafted, all study methods were reviewed and approved by the participating IRBs, but data collection not yet started.

2.2 Study Objectives

The primary objective of this study is to assess the effects of the WISH program on smoking abstinence and quit attempts relative to standard care. We hypothesize that WISH participants will be more likely to make a quit attempt and more likely to quit smoking. Secondary objectives include comparing randomization groups' markers of HIV severity (CD4 count) and HIV viral load and mortality risk (calculated using the Veterans Aging Cohort Study [VACS] Index)[34-37] at follow-up and comparing groups' intermediate change variables (such as motivation to quit and self-efficacy) at each follow-up. Finally, we will describe the reach and implementation of WISH by comparing Veterans willing to enroll vs. those who decline participation and comparing participants who use the provided treatments to those who do not.

2.3 Vanguard Cohort

The first 20 participants will be considered part of a vanguard pilot cohort. We will test our procedures with this cohort and make protocol modifications, as necessary. The *a priori* decision has been made to automatically exclude the first 2 participants randomized to each study arm from the final analytic sample, since these individuals are more likely to experience issues with the study implementation which could bias their outcomes. Subsequent vanguard participants will be retained in the final analytic sample provided no significant protocol changes are made or issues encountered which reasonably bias outcomes. We will consult with the DSMB to make a determination whether to retain the remaining 18 participants in the final analytic sample or not.

2.3 Recruitment and Eligibility Criteria

Participants will be recruited from the national VA health care system, the largest integrated health care system in the U.S. and the nation's largest provider of HIV care. Potential participants will be initially identified through the VA Corporate Data Warehouse (CDW) by first identifying all patients with a diagnosis of HIV based on ICD codes. These patients will then be filtered based on their utilization of VA services (identified using stop-codes). Those who came to a primary care and/or infectious disease clinic or telehealth visit, or had an inpatient hospital stay in the prior two years will be retained. Next, we will identify active smokers in this sample using "Health Factors" data that are documented in the EHR in response to an electronic clinical reminder that is used nationally in VA to screen for tobacco use.[38] Finally, we will exclude any patients living outside of the mainland U.S. and anyone with an ICD code indicating serious cognitive impairment or mental illness, including dementia or psychosis.

Those who meet the inclusion criteria will be mailed a study invitation letter including an opt-in or out card that they can mail back to indicate if they are interested in learning more or participating in the study. Those who do not opt out will be contacted by phone to be screened for eligibility. Individuals will be considered provisionally eligible if they report currently smoking five or more cigarettes per day, are HIV-infected, receive health care within the VA, and have a personal cell phone that can receive text messages. Individuals will be excluded if they report currently receiving treatment for smoking cessation or have significant trouble hearing such that it would limit their ability to engage in the phone-based

counseling. Final eligibility will be based on completing the baseline interview. Individuals who screen eligible and consent to participation, but fail to complete this interview, will not be enrolled in the study.

2.4 Consent, Baseline, Randomization and Enrollment

Individuals who pass the eligibility screen will provide informed consent to participate and then complete the baseline phone interview. Afterwards, participants will be randomized to treatment using an automated algorithm built into the REDCap assessment system. Randomization will be stratified by two survey questions which assess the number of cigarettes participants smoke per day (10 or fewer cigarettes per day vs. >10) and their current readiness to quit smoking (ready to quit within 30 days versus not ready to quit within 30 days). After participants are randomized, they will be informed of their treatment assignment. Control arm participants will be referred to contact the National VA Quitline. Experimental arm participants will contacted by a study counselor to initiate their intervention.

2.5 Blinding

As is typical in behavioral intervention studies which involve live counseling or study contact with participants to collect follow-up data, it is not possible for all staff to remain fully blinded in this trial, but we will take the following steps to minimize the risk of bias that could result from this. For example, usual care counselors in the control arm will be blinded and not informed of participants' enrollment in this trial. In the experimental arm, counselors, fidelity coders, and staff over-seeing fidelity monitoring will be blinded to the identity of participants in the control arm and will not have access to study outcome data. Follow-up data collection will be done via online surveys and participant responses will be directly entered by participants. If phone follow-up is needed to complete data collection, interviewers will be blinded to the participants' study arm. Finally, the study investigators will not have access to unblinded interim study reports shared with the DSMB.

2.6 Intervention

2.6.1. Control Intervention.—The control intervention includes standard tobacco quitline services provided by the National VA Quitline (QuitVET; 1-855-QUIT-VET) and access to the SmokefreeVET text messaging program. The telephone counseling is grounded in social cognitive theory and cognitive behavioral therapy (CBT) and includes a focus on the standard counseling components demonstrated effective for CBT-based tobacco cessation treatment: motivational enhancement, social support, problem-solving, coping skills training, and decision support for cessation medications. QuitVET callers receive up to 9 counseling sessions, with proactive callbacks available after the first session. The first call typically lasts 15-30 minutes and subsequent call duration is about 5 minutes.

In addition to telephone quitline counseling services, control participants may also enroll in the Smokefree VET text messaging program. This program is designed for tobacco users who are ready to quit. Veterans can enroll to receive text messages up to 2 weeks prior to their planned quit date. The messaging program includes 3-5 messages per day for 6-8 weeks, depending on the timing of the chosen quit date. In addition to these

standard messages, Veterans can also access on-demand message content in specific areas using keywords (URGE, STRESS, SMOKED, DIPPED), including a keyword (CRISIS) that connects the user to the Veterans' Crisis line for help with distress or suicidal thoughts. Content of the SmokefreeVET text messaging program is consistent with the content of the telephone counseling.

The control intervention is similar to the experimental intervention (WISH) in that it offers proactive telephone counseling sessions, a text-messaging program, and referral to participants' VA healthcare team to assess medication appropriateness and receive a prescription. Key differences between the two interventions are the amount of contact and the content focus. Control participants receive significantly more text messages, but less counseling contact than planned for the experimental arm (approximately 1 hour versus approximately 3 hours). Additionally, the control intervention focuses exclusively on tobacco use and cessation, whereas the experimental intervention will address a variety of health-related topics, as discussed below.

2.6.2. Experimental Intervention.—WISH is designed as a comprehensive, patient-centered, wellness intervention that targets motivation for quitting and cessation (primary goals) while also targeting other HIV-related self-management topics such as treatment engagement, depression, stress management, and other substance use/abuse. The intervention is guided by the Information-Motivation-Behavioral Skills Model of Smoking Cessation [39] and incorporates Motivational Interviewing [40] and CBT-based strategies for addressing smoking and other health behaviors. By imbedding the smoking-related content into a comprehensive self-management program, the intervention is intended to foster greater engagement for PLWH, particularly those ambivalent about quitting at enrollment.

WISH includes 6 telephone counseling sessions, each designed to last 20-30 minutes. Participants will receive a brief reminder text prior to each scheduled call, a follow-up text message after each call, and a final check-in text message approximately one month following counseling completion. The texts sent between counseling calls will outline the participants' action plan for the coming week and acknowledge their personal health goals. Counselors will use a standard framework for drafting all text messages to ensure consistency across individuals, but the details of each message will be tailored to the participant. Sample texts might look like:

> Hi John. Just a reminder of our next call tomorrow at 8 am. I look forward to hearing more about your plan to be more physically active. -Pat from the WISH study
>
> Sam – Today is your target quit day. Remember to use the ACE strategies we discussed and your nicotine gum. I look forward to hearing how the day goes when we talk next. – Pat from the WISH study

Counselors may acknowledge and briefly respond to texts from participants to acknowledge and reinforce their action plans for change, but two-way texting will not be used as a substitute for counseling or problem-solving with participants. To protect confidentiality, no

personal health information or other sensitive information will be included in texts sent to participants.

Between counseling sessions, participants will be also asked to engage in a series of short, motivational and skills-building exercises called “personal experiments.” As the name implies, participants are encouraged to try each experiment and see what they learn from it. The exercises are aligned to the content planned for each counseling session, which follows this outline:

Session 1: Healthy living priority setting and treatment engagement. The goal of session 1 is to engage participants in mutually agreed upon tailored treatment plan for their self-care, including a commitment to address various wellness topics of interest, including smoking.

Session 2: HIV specific and general smoking cessation information. The goal of session 2 is to build motivation for quitting smoking by providing HIV-specific information on the health risks and benefits of cessation and other motivational information (including COVID-19 risks related to smoking and HIV). “Personal experiments” to support behavior change are also introduced in session 2. These intersession exercises are designed to build motivation for change or teach skills relevant to quitting smoking.[41] New experiments are introduced in each subsequent session.

Session 3: Psychosocial influences on personal health behavior goals. The goals of session 3 are to explore the relation between stress, mood, and social support with smoking and other personally relevant health behaviors (e.g., treatment adherence, physical activity, nutrition) and to facilitate coping skills training and improved self-care.

Session 4: Other substance use influences on cessation and other personal health behavior goals. The goal of session 4 is to discuss stimulus control strategies for smoking cessation and HIV management, with specific emphasis on use of drugs and alcohol as personally relevant.

Session 5: HIV-related and cessation-related treatment adherence/care management AND continued motivation/skills building. The focus of session 5 is on improving treatment adherence and care management. Health status and its relation to smoking are addressed, including as related to immune function. Smoking cessation content continues to be tailored to stage of change in this session and, if appropriate, the personal experiment selected may include a practice 24-hour quit attempt.

Session 6: Smoking cessation relapse prevention, building self-efficacy for smoking cessation and HIV self-management AND Wrap up, future resource identification, and long-term planning. In the final session, goals include introducing relapse prevention skills training, encouraging continued personal experiments to foster self-efficacy for quit attempt/sustained quitting, reinforcing progress toward health goals, and identifying available resources to support sustained cessation goals.

Finally, as in the control condition, participants who are ready to quit smoking will be encouraged to request a standard course of FDA-approved pharmacotherapy from their VA healthcare team. Medication choice, duration, and dose will be determined by participants' health care providers.

2.7 Fidelity Monitoring

Fidelity will be monitored in two ways. First, counselors will track their adherence to the protocol following each session using a standardized checklist of key session content. If content could not be delivered as planned, they will note this and the reason (e.g., call dropped, participant refused). Second, experimental calls will be randomly selected for review using a predetermined algorithm designed to ensure that a minimum of 10% of each session type (one through six) for each counselor is reviewed. The fidelity rater is trained in CBT, motivational interviewing, and the WISH protocol. The coder will use a standardized checklist of key treatment components to document how well the intervention call content adheres to the session's planned protocol. Each topical component will be rated as: fully discussed as planned, partially discussed, or absent. The reviewer will also assess the extent to which the counselor adheres to the spirit-of motivational interviewing (e.g., appropriate use of open-ended questions, affirmations, reflections and summaries)[40] and overall fidelity of the session content to the intervention manual. Instances when content is absent or only partially discussed will be routinely reviewed with the counselors to guard against protocol drift. Text messages will also be reviewed to ensure compliance to the delivery protocol and HIPAA-compliance with privacy protections. The latter is important since text messages are not pre-scripted.

2.8 Assessment Methods

2.8.1 Assessment Contacts.—Participants will be surveyed at baseline and 3- and 6-months post-enrollment. All follow-up assessments will be conducted using an online REDCap survey with phone follow-up for non-responders. Each assessment is designed to take approximately 20 minutes.

2.8.3 Measures.—Baseline variables include demographics (such as age, race, gender, education) and nicotine use history (including tobacco products and e-cigarettes), smoking cessation treatment history, and past quit attempts assessed using standardized items from the 2017 and 2018 Behavioral Risk Factor Surveillance Surveys [42, 43], the 2015 Tobacco Use Supplement to the U.S. Census Bureau's Current Population Survey [44], and the International Tobacco Control Four Country Survey on smoking and vaping [45]. Additional standardized measures assess nicotine dependence (FTND) [46], alcohol use (AUDIT-C) [47], use of marijuana and other substances (ASSIST-Lite) [48], and current depression (PRIME-MD) [49]. Motivation, self-efficacy for quitting smoking, and perceived importance of quitting smoking will be assessed using 10-point Likert scales ranging from "not at all" to "very." Stage of readiness for quitting smoking will also be assessed.[50, 51]

HIV-specific smoking information will be assessed using a brief scale used in our prior work which assesses knowledge about how smoking impacts HIV disease course and HIV treatment response [33]. History of COVID-19 diagnosis and smoking-related beliefs about

COVID-19 will be assessed using brief items developed for this study (e.g., beliefs that COVID-19 is riskier for people living with HIV, for smokers, or Veterans; changes in motivation to quit smoking related to COVID-19). Key outcome, mediator, and moderator variables which are subject to change will be re-assessed at 3- and 6-month follow-up.

Primary outcomes are (a) self-reported presence of any 24-hour intentional quit attempt (assessed as, "During the past 3 months, have you stopped smoking for one day or longer because you were trying to quit smoking?" [yes/no]) [44] and (b) 7-day point prevalence smoking abstinence (7-day PPA; assessed as, "Have you smoked a cigarette, even a puff, in the last 7 days" [yes/no]).[52] PPA is used to facilitate comparison of outcomes with prior published trials, since PPA is the most commonly reported abstinence measure.

Secondary smoking outcomes include number of cigarettes per day, 30-day PPA, and floating prolonged abstinence, in which the starting point "floats" based on one's actual quit date rather than a pre-defined target quit date.[53] This is preferable for studies which do not have a pre-set quit date for participants and recognizes that multiple quit attempts may be made before abstinence is sustained. We will examine the longest period of abstinence following study enrollment. Criteria will be met for prolonged abstinence if this attempt lasts 3 months or longer at 6-months follow-up. Number and duration of other quit attempts will also be assessed at each follow-up using standardized items from the 2015 Tobacco Use Supplement to the Current Population Survey.[44] Finally, smoking abstinence will be biochemically confirmed using salivary cotinine among a random sample of participants who report abstinence at follow-up.

Additional self-report follow-up measures will include cessation treatment use (including use of counseling or medications) and adherence, and other usual care cessation treatment utilization. Each will be assessed using measures from prior published studies.[54, 55] Participant-level clinical data will be obtained from the VA's CDW and VACS databases. This includes most recent CD4 count, VACS Index 2.0 of mortality risk [37], most recent HIV RNA level, antiretroviral medication, HIV-related co-infections (e.g., HPV; Hep B & C) and relevant comorbidities (e.g., COPD; non AIDS-defining cancers including lung cancer, anal cancer, Hodgkin lymphoma). The VACS Index is a validated, generalizable risk index for predicting allcause mortality that uses routine clinical laboratory data and is responsive to change, such as after initiation of ART. [34, 35] We will assess change in VACS index and other variables over the course of the intervention and to 12-month follow-up.

2.8.4. Biochemical confirmation.—We initially planned to confirm smoking status among all participants who reported smoking abstinence at 6-month follow-up, but due to NIH funding cuts at the time of award, the plan was altered with the approval of NCI program officials to only collect this data among a randomly selected subset of 20% of smoking abstainers in each arm. This was a pragmatic decision based on resource availability, but a 20% sample was deemed adequate to compare disconfirmation rates between arms, to ensure that false reporting does not differ by intervention group. It will not be used to establish cessation rates in either arm. Rather, we will track and compare the number of people in each arm who misreport smoking status or fail to complete the cotinine test.

Because cotinine level is affected by use of nicotine containing products such as NRT and e-cigarettes, we will also assess recent use of any nicotine-containing products and re-assess smoking status at the time of the cotinine test. This information will further inform if discordance between self-reported smoking status and cotinine level is due to false reporting or continued nicotine use. If observed cotinine levels appear related to use of nicotine-containing products other than tobacco in the past week, self-reports of not-smoking will be considered accurate and not counted as false reports.

Cotinine levels will be assessed using a saliva dipstick and test completion remotely monitored using VA Connect, a secure online video link provided by the VA. Prior to the completion of the test, we will confirm individuals' identities. Following completion of the test, we will capture a video screenshot of the saliva test strip and the final test result, which will be saved and interpreted by a member of the research team who is blinded to each participants' randomization arm.

2.8.5 Retention Strategies and Incentives.—Participants will receive mailed and emailed reminders prior to each scheduled follow-up survey. Individuals who fail to complete the online survey within approximately 2 weeks will be called to complete the interview by phone. All respondents will receive a $20 thank you gift card. Participants who complete the biochemical confirmation will also receive an additional $20 incentive. Participants lost to follow-up will be tracked using contact information from the VA.

3. Planned Analyses

3.1 Study Hypothesis.

Our primary hypothesis is that the WISH intervention will be more effective at promoting quit attempts and long-term smoking cessation at 6-month follow-up (our two co-primary outcomes) than standard care. Other planned analyses of secondary outcomes will be descriptive or exploratory.

3.2 Primary Analyses of Smoking Outcomes

3,2,a. Smoking Abstinence.—We will use chi-square analyses to compare the percentage of participants in each arm who are abstinent using our primary cessation indicator: 7-day PPA at 6-months. These analyses will also be run using logistic regression to control for the baseline variables used in the block randomization (baseline intention to quit within 30 days, baseline number of cigarettes smoked per day <10), since failure to do so can result in biased estimates of the treatment odds ratio. Conclusions about efficacy of the intervention will be based on adjusted odds ratios from the regression models.

Participants will be analyzed based on their assigned randomization arm, regardless of their utilization of the provided intervention (intent to treat methodology). Following the Russel Standard [56], unless known to be deceased, respondents who are missing abstinence outcome data will be classified as smokers in the primary analysis. To assess the robustness of trial findings to potential associations between missingness and the unobserved outcomes, Jakobsen [57] and Little [58] recommend performing sensitivity analyses under plausible Missing Not at Random (MNAR) mechanisms. We will use the approach outlined by

Hedeker et al. [59] to assess the sensitivity of study findings to deviations from the assumptions of the Russel Standard. Hedeker's approach is preferred because it uses a straightforward parameterization of the MNAR mechanism in terms of an odds ratio that determines the strength of the association between missingness and the smoking outcome.

3.2.b. Quit attempts.—To assess intervention effects on 24-hour quit attempts, we will analyze this outcome both as a binary measure (none vs. 1+ attempts) and as a count of number of quit attempts. For the binary measure, we will conduct unadjusted chi-square tests and adjusted analyses using similar logistic regression models as described above but with the addition of baseline number of quit attempts in the prior year. For the count version of this measure, we will conduct unadjusted analyses comparing the mean number of quit attempts by group using t-tests/Wilcoxon tests and conduct adjusted analyses using similar models to that above (i.e., either ordinary least-squares regression or Poisson regression). The final choice will depend on the shape of the distribution of quit attempts. If quit attempt status is unknown, we will assume that the person made no quit attempts.

3.3 Secondary Analyses of Smoking Outcomes.

We will use similar analyses to that described above to assess group differences in our secondary smoking outcomes: 7-day PPA at 3- months, number of cigarettes smoked per day 30- day PPA at 3- and 6-months, and floating prolonged abstinence at 6 months. Unadjusted analyses will use chi-square for binary measures and t-tests/Wilcoxon for means. We will then conduct reduced and fully adjusted models using logistic regression for binary outcomes and least-squares or Poisson regression for means. 7-day PPA at 3- months will be analyzed using a logistic regression model, adjusting for baseline variables used in block randomization. To test the effect of the intervention on 30-day PPA and cigarettes per day over the entire course of follow-up, data on these outcomes from both 3- and 6-month follow-up will be analyzed using generalized estimating equations (GEE) regression models to account for within-subject correlation over time. For 30-day PPA, we will use a logistic regression model. For cigarettes per day, we will use a Poisson regression model. We will adjust for baseline variables used in the block randomization as well as time in both secondary outcome models. We will quantify a potential non-constant intervention effect over time by including a time-by-treatment interaction term. If there is sufficient evidence of a non-constant intervention effect, we will use 6-month follow-up as the primary time point of interest for 30-day PPA and cigarettes per today. Otherwise, we will use the GEE regression model to estimate the effect of the intervention using the entirety of the follow-up data. Floating prolonged abstinence at 6-month follow-up will be analyzed using the method proposed in Aveyard [53]. This method estimates the probability of 3-month sustained abstinence initiated during the treatment phase based on a combination of the number of people with 3-month sustained abstinence during the six month follow-up period and the number of people who may have had 3-month sustained abstinence but whose outcome cannot be determined due to censoring at the end of follow-up (e.g. those who have been abstinent for 2 months at the end of follow-up). The contribution of the censored individuals to the estimate of 3-month sustained abstinence is weighted by the probability that they would have gone on to be abstinent for three months had follow-up continued.

3.5 Secondary Analyses of Process Change Variables.

Change in intermediate change process variables (i.e., HIV specific knowledge, self-efficacy, motivation for quitting smoking, use of cessation medications) will be analyzed using similar methods to that described above. We will start with unadjusted analyses using chi-square for binary outcomes and t-tests/Wilcoxon for means, then conduct reduced and fully adjusted models using logistic regression for binary outcomes and least-squares or Poisson regression for means. For outcomes assessed at baseline and follow-up, adjusted models will include the baseline measure. As needed, data will be transformed to account for possible left or right skewness. We will also test if the effect of the intervention on these intermediate variables is constant across the two follow-ups using GEE.

3.6 Secondary Analyses of HIV-related Outcomes.

Analyses of secondary HIV-related outcomes will use similar unadjusted and adjusted method described above. For outcomes such as CD4 count and VACS Index scores with baseline and follow-up measures, adjusted models will include the baseline measure.

We will compute the VACS Index using the 2.0 version based on the following variables obtained from the VA databases: age, CD4, HIV-1 RNA, hemoglobin, alanine and aspartate transaminases, platelets, creatinine and hepatitis C virus serostatus, albumin, white blood count, and body mass index. [37] 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.[37] 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, which may be due to smoking reduction, smoking cessation and/or other health behavior changes made as a result of the intervention.

3.7 Descriptive and Additional Group Comparisons

Descriptive and bivariate analyses will be used to characterize the 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 study, 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.

3.8 Sample Size Considerations

With a sample of 500, using an intent to treat model, and imputing non-responders as smokers, if we observe a base rate of 10% PPA in the control arm at 6-month follow-up, we will have at least 80% power to detect a clinically important difference (i.e., 7% or greater) in smoking abstinence between randomization arms. 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 able to detect a clinically significant difference of 10% with 80% power. With respect

to quit attempts, we expect 20% to 25% of control participants will make an intentional quit attempt. If this is 20%, the difference detectable with 80% power will be 12.3% (20% vs. 32.3%), OR=1.91. If the rate in the control arm is 25%, the detectable difference will be 13.0%.

4. Summary and Discussion.

This manuscript provides an overview of the rationale, design, and methods for the WISH trial, one of seven recent studies funded by the National Cancer Institute to advance our understanding how to more effectively promote and support smoking cessation among SLWH.[32] To date, there has been a relative paucity of randomized trials conducted in this high-risk population, despite the critical importance of smoking cessation among SLWH and reasonable evidence that these individuals would benefit from interventions tailored to their unique needs. It is our hope that WISH, along with our colleagues' ongoing studies and future trials funded by NCI, will ultimately provide the evidence-base needed to reduce smoking among this medically vulnerable patient population. This protocol is offered to assist others interested in this work.

We should also note that, as with many randomized trials which were initially scheduled to launch in 2020, recruitment for this study was delayed as a result of the SARS-CoV-2 pandemic and its cascading impacts across the participating study sites. At present, launch of the vanguard pilot is expected in the spring of 2021, followed by launch of the main trial in the summer. Other than modifying the WISH intervention and assessment measures to address COVID-19, no other methodological changes were needed in response to the pandemic. The trial was always designed to be remotely delivered, allowing us to recruit from a nationwide sample and to mirror the delivery of standard care via the VA Tobacco Quitline and SmokeFree VET interventions. As a result, if the intervention is found to be effective, it could be adopted by the VA Quitline or other tobacco quitline providers. The fact that the WISH intervention has been designed for large-scale dissemination is a strength of this research study. Our inability to conduct broader biochemical verification is an acknowledged study constraint, but this design change was necessitated by funding cuts and beyond the research team's control.

In sum, we believe this protocol may be useful to other researchers interested in novel approaches to promoting smoking cessation, remotely-delivered interventions, and treatment programs targeting SLWH or veterans.

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Abbreviations:

AIDS	acquired immune deficiency syndrome
ART	anti-retroviral therapy
ASSIST-Lite	Alcohol, Smoking and Substance Involvement Screening Tool - Lite
AUDIT-C	Alcohol Use Disorders Identification Test
CDW	Corporate Data Warehouse
COVID-19	Coronavirus Disease 2019
DSMB	data and safety monitoring board
EHR	Electronic Health Record
GEE	Generalized Estimating Equations
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
ID	Identifier
IMB	Information-Motivation-Behavioral Skills
KPWHRI	Kaiser Permanente Washington Health Research Institute
NCI	National Cancer Institute
NRT	nicotine replacement therapy
PLWH	People living with HIV
PPA	point prevalent abstinence
RNA	ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SLWH	Smokers living with HIV
VA	Veterans' Administration
VACS	Veterans Aging Cohort Study
WISH	Wellness Intervention for Smokers Living with HIV
UCD	University of California, Davis
UW	University of Washington

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