2. SPECIFIC AIMS

Tobacco use has emerged as a leading cause of death in persons living with HIV (PLWH). Improved survival resulting from highly active antiretroviral therapy is tempered by **alarming increases in non-AIDS related malignancies**,[1-3] **most notably lung cancer**.[2,3] Of the more than 1.1 million PLWH in the US,4 60% smoke cigarettes,[5] and 75% are interested in quitting.[6] Almost none of them are accessing behavioral cessation treatments, and programs targeting their specific needs are virtually non-existent.[7] NIH and USPHS have highlighted this public health need and have identified smoking cessation in PLWH as a leading priority.[8,9]

The Internet has emerged as an important route for tobacco treatment delivery.[10] Web-based interventions offer smokers convenience, low (or no) cost, anonymity, and are effective in promoting abstinence.[11] Today, most national and state public health agencies (including the NCI) offer web programs as integral components of their tobacco treatment portfolios. [[In a national sample, 13% of US smokers reported seeking online assistance to quit within the past 12 months.[12] With such broad potential reach (and low cost) even small increases in quit rates can have a large public health impact. **At the time of this submission, there is not a single web-based treatment targeting PLWH smokers available in the US or elsewhere. This represents a health disparity of the first order, and a public health opportunity missed.**]]

Positively Smoke Free on the Web (PSFW) is a static, 8-session, theory-driven, culturally-tailored web-based program developed by our team to address the unique needs of PLWH smokers. Our NCI-funded R21 pilot trial of PSFW demonstrated moderate-high levels of adherence to the program schedule, and the PSFW condition exhibited higher 3-month abstinence rates than standard care (10% vs. 4%).[13,14] Among those who completed all 8 sessions, 18% achieved abstinence. [[These pilot data compare favorably with web-based treatment outcomes reported from large, general-population studies (see 3.A.4), they support the feasibility of web-based tobacco treatment for this underserved and vulnerable group, and they provide justification for a more definitive study of a very promising intervention.]]

Social support is a critical component of tobacco treatment.[15] Research by our team and others has demonstrated the positive impact of social network participation on smoking cessation.[16-19] **Smokers who participate in an online community – whether passively reading posts by others or actively engaging in online discussions – are more than twice as likely to achieve abstinence even after controlling for a broad range of covariates.[20]** Specifically for PLWH, an online community offers an anonymous and accessible platform to exchange support, to share information and cessation strategies, and potentially to overcome the loneliness and lack of network support for quitting which we have shown to be important drivers of smoking and obstacles to quitting.[21-23] Establishing a functional and therapeutically effective online community requires time, purposeful planning, and careful nurturing.[24-26] Behavior intervention studies that have attempted to evaluate the effectiveness of online communities created synchronously with trial initiation have met with limited success.[27-29] In preparation for this trial, The American Legacy Foundation (Legacy) – a partner on the proposal and leader in the field of online social networking for cessation – has already established and alpha and beta-tested a prototype online community including a core group of fully-trained seed users as an integrated component of PSFW (now "**PSFW+**"). These efforts ensure that by trial launch we will be prepared to achieve the following **Specific Aims** and test a priori hypotheses (H):

Aim 1. To **test the efficacy of PSFW+** compared to an attention-matched web-health intervention (American Heart Association Getting Healthy) in achieving 7-day point prevalence abstinence (ppa) at 6 months post-randomization in a cohort of PLWH smokers (N=550). All subjects will be offered nicotine patches. *H1: PSFW+ will yield higher abstinence rates than the control intervention at 6 months.*

Aim 2. To examine whether the impact of treatment condition on cessation is **mediated by greater perceived social support** afforded by the PSFW+ program. This central aim is supported by our work with PLWH that has shown strong associations between loneliness, smoking, and lack of social support for quitting.[22,23] *H2: Intergroup differences in 6-month abstinence will be mediated by greater changes in perceived social support among those in PSFW+.*

Exploratory Aim: To explore moderators and additional mediators of treatment efficacy. Potential moderators of interest include gender, education, age, race, HIV risk category, depression, anxiety, other substance use, and stigmatization.[30] Potential mediators identified in our previous work include nicotine replacement use, dose of intervention, and changes in abstinence self-efficacy.[23,31-33] These analyses will draw upon the experience of the investigative team in assessing complex mediation effects[33,34] with particular attention to PSFW+ utilization metrics.

This proposal brings together leaders in HIV/tobacco use and a technology team at the forefront of health-related social networking to leverage investments already made by NCI and Legacy in the creation and piloting of PSFW. It will retain all of the empirically-tested content of the original website and enhance and modernize it with the power of

social media. Establishing the efficacy of a web-based smoking cessation program for PLWH that has broad reach would not only represent an enormous advance in the fight against tobacco use in PLWH, but would also provide a clearer understanding of the role of targeted, web-based health interventions in comprehensive HIV care.

3. RESEARCH STRATEGY

3.A. SIGNIFICANCE

3.A.1. Tobacco Use is a Leading Cause of Death Among Persons Living With HIV (PLWH). Since the advent of highly active antiretroviral therapy (HAART), deaths from AIDS-defining infections and neoplasms have diminished dramatically, while non-AIDS defining cancers have become increasingly important causes of morbidity and mortality.[35] Among these, lung cancer is the leading killer, causing 22% of cancer-related deaths among PLWH in the US during the HAART era.[2] Outside the US, a large European PLWH cohort recently reported a standardized mortality ratio for lung cancer of 5.85.[3] The heavy toll that lung cancer exacts on PLWH is believed to be primarily attributable to high rates of tobacco use.[36,37] More than half of US PLWH smokes cigarettes.[5,6] In a cohort of 5,472 PLWH, tobacco use accounted for 24.3% of deaths and 30.6% of all non-AIDS defining cancers (including skin cancers).[37] On average, over 12 years of life are lost as a direct result of tobacco use in PLWH smokers.[38]

3.A.2. Developing Effective Smoking Cessation Interventions for PLWH is a Priority. Smokers living with HIV suffer from high rates of nicotine dependence, anxiety and depression, loneliness, and comorbid substance use.[39] [[Depression and anxiety are hyperprevalent among PLWH smokers, and we have shown them to be intertwined with other behavioral barriers to quitting such as low abstinence self-efficacy[31] and loneliness.[22]]] Although most are interested in quitting, only a small proportion of PLWH smokers who participate in clinical trials that include nicotine replacement therapy (NRT) sustains abstinence at 6 months[40] compared to 20-30% quit rates seen with similar treatments in the general population.[41] To date, only a handful of sufficiently powered smoking cessation trials have been conducted with PLWH smokers, and abstinence outcomes at 6 months have not exceeded 12%.[6,39,42-44] One exception was a recent 3-arm study comparing intensive individual counseling, static web-based tobacco treatment, and a minimal contact control that reported anomalously high 3-month quit rates in all conditions (26%, 29%, and 24%, respectively) with no significant between group differences.[45] Both NIH and USPHS have designated smoking cessation among PLWH as a priority given the high rates of cancer and smoking-attributable disease.[8,9]

3.A.3. Web-Based Cessation Programs can Reach PLWH Smokers. Most PLWH smokers want to quit,[6,39] but poor physical and mental health, transportation, cost, stress associated with coping with their illness, conflicting medical appointments, and scarcity of tobacco treatments in HIV care settings comprise a unique constellation of barriers that PLWH smokers face in accessing cessation programs and achieving abstinence. Web-based interventions could dramatically increase access for PLWH smokers: data from our previous work in 2010-2011 revealed that over half of smokers living with HIV had home access to the Internet and that number has been growing rapidly **(3.C.1.e.)**.[46,47] A just-published survey of inner-city women living with HIV in 2014 reported that 75% participated in web-based social networking and 48% participated in health-related social networking.[48] Web-based smoking cessation interventions have been tested in dozens of randomized trials[11,49-51] but only the aforementioned study by Humfleet and colleagues specifically addressed PLWH smokers.[45] Atypically high cessation rates in all study conditions (including the minimal contact control group) make it difficult to draw conclusions from this trial.[45]

There is convincing evidence of the effectiveness of computer- and web-based interventions for health behavior change among PLWH in areas other than smoking. In a study examining the psychological effects of general online support group use for PLWH, subjects with higher levels of participation had better psychological health than those with lower levels of participation.[52] Structural equation modeling revealed that greater use of an online support group was associated with more frequent occurrence of empowering processes as measured by receiving useful information, receiving social support, finding positive meaning and helping others.[53] These empowering processes were related to higher levels of adaptive coping, which in turn were related to higher quality of life.[53] Computer-based interventions are also effective at promoting medication adherence[54-56] and depression symptom management[57] among PLWH. Meta-analytic data support the efficacy of web-based HIV-prevention for persons at risk for HIV.[58] These various studies have also reported high levels of engagement and satisfaction with web-based programs.

[[In the general population, utilization of web-based programs dwarfs all other modes of behavioral tobacco treatments.[27] The most recent national survey of tobacco treatment utilization, conducted in 2007, indicated that 13% of US smokers had sought assistance in quitting online within the past year[12] – a proportion that has likely risen by 2015 with the expansion of internet's reach and the continued proliferation of restrictive smoking policies and tax increases. **If 13% of the 660,000 PLWH smokers in the US were to access an effective web-based program and**

10% of them stopped smoking, this would translate into 8,580 successful quitters and (assuming a 45% reduction in mortality as a result of quitting[38]) over 47,000 years of life saved.[38] At the time of this submission, there is not a single web-based program targeting PLWH smokers available in the US or elsewhere. This represents a health disparity of the first order, and a public health opportunity missed.]]

3.A.4. Our Web-Based Cessation Program for PLWH Showed Preliminary Evidence of Efficacy. Our R21 trial (R21CA163100-01) was a feasibility and efficacy pilot of Positively Smoke Free on the Web (PSFW). With input from HIV specialists, behavioral psychologists, graphic artists, software engineers, and PLWH smokers, we distilled the theory driven and culturally tailored content of our group counseling smoking cessation curriculum for PLWH[21] into a static web-based intervention (**3.C.1.e.**). An intensive protocol designed to maximize engagement was implemented, comprised of email/text reminders to return to the program as well as clinic-based telephone outreach to participants who were non-adherent. The study demonstrated initial feasibility and efficacy: 2/3 of subjects logged into ≥6 sessions, and 40% logged into all 8 sessions. Preliminary efficacy analyses suggested that higher program completion rates were associated with increased cessation. The majority of participants (73.9%) elected to receive text messages in addition to email reminders and the vast majority of users (94.2%) received live phone call reminders. At 3 months, 7-day point-prevalence abstinence (**ppa**) was 2.3 times higher in PSFW compared to SC (10.1% vs. 4.3%). [[Although the trial was not powered to detect a significant difference of this magnitude, these results are promising when viewed against the background of the available evidence base. In the largest meta-analysis to date,[59] which included 77 RCTs of computerized/electronic tobacco treatments, the odds ratio for successful quitting was 1.32 (1.21-1.45) for those randomized to the experimental interventions, and the rate of long-term abstinence with these interventions (10.9%) was very similar to the 10.1% that we reported, Moreover, the dose-response effect that we observed is further evidence of program efficacy. An effect of this size generated by a wide-reach, low-cost intervention can have a large public health impact.[60] Consistent with this view, the USPHS concluded that web-based tobacco treatment is "a highly promising delivery system…given the potential reach and low cost.[9]"]] The current proposal aims to conduct a definitive trial of our enhanced version of PSFW, with strong pilot evidence to support the hypothesis that PSFW+ will be efficacious and promises to expand the short list of evidenced-based treatments available to PLWH smokers.

3.A.4.a. PSFW Addresses Anxiety and Depression. [[The website repeatedly discusses the challenges of smoking cessation in the setting of psychiatric illness, urges users to seek mental health support, and emphasizes that smoking is an unhealthy strategy to manage these stressors. Interestingly, in the pilot trial of PSFW,[14] higher anxiety scores were associated with greater website utilization, even when adjusted for a range of covariates. It is possible that a web-based intervention may offer special benefits to the 62% of PLWH smokers suffering from anxiety disorder.[39] **Both anxiety and depression are recognized as key user characteristics in the design of the intervention, they are specifically addressed in the didactic content and the online community, they will be explored as putative moderators of program efficacy in the analytic plan, and their clinical implications are incorporated into the Protections against Risks plan (5.B.).**]]

3.A.5. Engagement in Online Social Networks for Cessation Promotes Abstinence. Adding an online community to PSFW may significantly enhance its efficacy and overall impact on quit rates. Intra-treatment social support is a critical component of "offline" smoking cessation treatment.[15] Our work in online social networks for cessation over the past 15 years has shown that individuals who participate in an online community in web-based smoking cessation programs – whether actively posting messages or passively reading communications among others ("lurking") – achieve higher abstinence rates, even after controlling for a range of covariates including baseline motivation to quit.[20,61,62] With the ubiquity of social media tools, "peer-to-peer healthcare" plays an important role in the healthcare landscape and health behavior change.[63-67]

3.A.5.a. Social Support as Mediating Process. Online social interactions may be particularly helpful for PLWH smokers given that loneliness is an important driver of PLWH-smoking behavior.[22] The Internet provides easy, round-the-clock access to "expert" patients – those further ahead on the tobacco treatment trajectory – who can provide firsthand experience about what might happen and how things feel[68] and can also provide empathic support and practical advice[63] about such matters as coping with cravings or slips, stress, anxiety, depression, and other substance use,[39] challenges especially common among PLWH. It transcends geography and the time constraints of traditional clinical scheduling to provide access to others coping with the same illness, taking the same medication, or navigating the same difficult behavior change. **This access is especially important for PLWH who may be struggling with isolation and stigma related to their diagnosis.[69]** Forming interpersonal relationships with similar others can create

a powerful sense of belonging, acceptance, empowerment, and comradeship, and can reduce the feelings of stigma.[68] Whereas a partner or family members may become burned out over a period of time, the flux and persistence of an online community means that there is always someone available for support. The relative "pseudonymity"[70] (disguised identity) of the Internet may also facilitate the exchange of support.[71,72]

3.A.5.b. Establishing a Functional Online Social Network Prior to Evaluation is Critical. Establishing an online community capable of providing the support theorized to impact cessation requires time, purposeful planning, and careful nurturing.[24-26] Simply making software available is not sufficient.[73] Keys to building a successful online community include enabling communication tasks to be motivating and meaningful for participants; devising software, moderator, and community-run strategies for encouraging online participation (e.g., meeting areas for new-comers); making participants aware of norms and responsibilities (particularly the need to contribute as well as take); making the community's purpose clear with a descriptive name and purpose statement; and facilitating the development of trust and empathy by allowing people to reveal themselves through stories and pictures.[74] Functional online communities are characterized by a variety of measurable characteristics including number of posts per member, number of replies, latency to first reply, thread length, percentage of members posting, members active within the past 30 days, and content popularity (e.g., 'likes').[75-77] Legacy's preparatory work integrating an online community prototype into the PSFW website and recruiting/training a critical mass of PLWH seed users to initiate and sustain community discussions **(3.C.4.e.)** will ensure the presence of a functional community in which to examine the study hypotheses.

3.A.6. Summary of Significance. An astonishing 61.5% of deaths among PLWH are attributable to smoking-related factors, and smoking reduces average total lifespan by 12.3 years.[38] Mortality risks were almost halved in ex-smokers.[38] Extraordinary advances in virology and pharmacotherapeutics have changed the face of the HIV epidemic, but the science of tobacco control lags far behind. There could hardly be a more urgent cause for the PLWH community than the development and delivery of effective tobacco treatment strategies. Few intervention studies are ongoing, and centers with the expertise and resources to conduct the broad-reach, scalable intervention research proposed herein are rare. This study promises to establish a new model of effective treatment for PLWH smokers that offers broad reach at low cost, and to significantly advance the science of tobacco treatment in this vulnerable group.

3.B. INNOVATION

Several aspects of the proposed project are innovative. **1) We are testing a new low-cost, broad-reach option for PLWH smokers seeking to quit.** PSFW+ represents the first web-based smoking cessation program to be introduced into the public domain for PLWH. More than 30 years into the HIV epidemic, PLWH smokers today do not have ready access to a single evidence-based behavioral tobacco treatment tailored to their unique needs. If proven effective, PSFW+ will represent a game-changing advance offering a broad-reach, scalable treatment to PLWH smokers with Internet access throughout the US. This proposal assembles a uniquely qualified group of investigators and technical staff, and leverages years of NIH-funded formative work to translate this vision into a reality. **2) Programmatic content is tailored to PLWH.** There is unequivocal evidence that web-based cessation interventions that incorporate increased message personalization and relevance are more effective than generic interventions.[11,78] PSFW session content specifically addresses the unique challenges faced by PLWH. It was developed through a painstaking, iterative process guided by the input of HIV-specialists, behavioral psychologists, tobacco treatment experts, web-developers, graphic artists, and PLWH smokers (including a Community Advisory Board). **3) A functional community will improve engagement and meet user expectations.** [[While retaining all of the original content, interactivity, and graphics of the original website, PSFW+ advances the functionality and potential efficacy of the PSFW core intervention via the incorporation of a social network. Although the traditional approach to the establishment of evidence-based interventions follows a new treatment through the pilot trial->definitive trial->dissemination pathway, the enhancement of PSFW was carefully considered by the investigative team. It leaves the original intervention completely intact, adds functionality that addresses additional needs of the target population (esp. social support, depression, and anxiety), and optimizes state-of-the-art social networking to ensure that this program is innovative today and will remain technologically relevant.]] Dr. Graham and her software development team at the American Legacy Foundation will fully integrate social networking features into PSFW, while retaining the program's fidelity to the theory-driven behavioral modeling components (esp. through observational learning and outcomes expectations). **4) PSFW+ is part of a suite of research-tested tobacco treatment options for PLWH.** PLWH smokers are a heterogeneous group, and it is clear that the response to the PLWH tobacco-use epidemic cannot be "one-size-fits-all." We intend PSFW+ described in this submission to be one item on a menu of smoking cessation treatment options for PLWH smokers. Dr. Shuter and colleagues have been funded by NCI, NIDA, and Legacy to

develop and test a range of Positively Smoke Free (PSF) products including a self-help brochure, educational materials for HIV care providers, a group treatment program, and a web-based intervention (PSFW). A mobile version designed for smartphones (mPSF) is in the development phase. We are honored that our PSF materials received the official endorsement of the late C. Everett Koop, MD, former Surgeon General. We envision PSFW+ as a key component in a PSF treatment menu for PLWH seeking readily-accessible, proven cessation strategies.

3.C. APPROACH

3.C.1. Prior Work. The multidisciplinary investigative team is led by Co-Principal Investigators **Cassandra Stanton, PhD** (Georgetown University; GU) and **Jonathan Shuter, MD** (Montefiore Medical Center; MMC, and the Albert Einstein College of Medicine; AECOM) who have collaborated on smoking cessation research in PLWH for the past 6 years. **Dr. Stanton** is a Clinical Psychologist and leading expert in tobacco dependence treatment among PLWH. She has been committed to understanding and developing interventions for tobacco dependence among PLWH for over a decade, with continuous NIH funding to advance programs that can best reach this diverse, heterogeneous patient population. **Dr. Shuter** is an infectious diseases/HIV-specialist physician and the Director of Clinical Research in one of the nation's largest HIV care centers. He has cared for his own panel of PLWH for over 25 years, and has led three NIH-funded tobacco treatment RCTs at his site. Co-Investigator **Princy Kumar, MD** (MedStar Georgetown University Hospital; MGUH) is the Division Chief of Infectious Disease at Georgetown University. She has developed one of the largest comprehensive treatment centers in DC, providing residents with multidisciplinary HIV care. She is a co-Investigator in an ongoing trial of group tobacco treatment for PLWH smokers, and is the PI of the Georgetown University AIDS Clinical Trials Group unit having conducted dozens of clinical trials within the MGUH HIV Clinical Program. **Ryung Kim, PhD** (AECOM) is a Biostatistician with expertise in the design and statistical analysis of clinical trials and mediation models within cancer control and prevention research. **Amanda Graham, PhD** (American Legacy Foundation) is a leading expert in the development and evaluation of web-based cessation interventions and online social networks for cessation. She is PI of a randomized trial (R01CA155489-01A1) focused on improving adherence to a web-based cessation program that informs the current proposal. The **Legacy software development team** has expertise in a broad range of software applications and was solely responsible for the modernization of the original PSFW project and integration of the community platform. [[**Clyde Schechter, MD (AECOM)**, is a recognized expert in health economics. He is working with Dr. Shuter in an ongoing trial of live group tobacco treatment and will assist the team in the estimation of incremental cost per quit associated with the PSFW+ intervention.]] The team and their respective organizations have an extensive history of productive collaboration and relevant experience. All investigators are NIH-funded clinical scientists with pooled expertise in HIV patient care, tobacco dependence treatment, clinical trials, web-based smoking cessation interventions, online social networks, and biostatistics. Relevant work that demonstrates their ability to achieve the aims of the study and pilot data on which the design and mediation models are built are summarized below.

3.C.1.a. Smoking cessation treatment challenges and social support needs among PLWH smokers. In a study of 444 US PLWH,[79] Stanton and colleagues reported high levels of nicotine dependence, elevated risk for depression, poor quality of life, and diminished social support; these findings are consistent with other studies among PLWH.[6,39,79,80] In a separate study focused on Latino PLWH smokers, Stanton et al.[81] found that heavy smoking was associated with low self-efficacy to quit, high nicotine dependence, high levels of depression, and low quality of life. In the MMC Infectious Diseases (ID) clinic, Dr. Shuter conducted in-depth interviews to explore numerous domains of smoking behavior among PLWH.[39] Key findings included: 1) 56% desired formal cessation treatment, 2) 75% had a history of depression, 3) 63% had a history of anxiety disorder; 4) 67% stated that smoking helped them cope with depression, anxiety, and/or anger, 5) 27% thought that smoking helped them fight infections and/or increased their CD4+ counts, 6) 33% reported at least moderate distress due to loneliness (8% moderately, 12% very, and 13% extremely lonely), and 7) 38% reported using cigarettes as a means of increasing social interaction. These results highlighted the unique needs of PLWH smokers and guided the initial development of the PSF program. [[The prevalence of depression and anxiety strongly influences the content of all PSF programs, and these key parameters are evaluated as moderators of intervention effects in our clinical trials.]] The prevalence of loneliness and use of cigarettes for social interaction suggest that PLWH may benefit from the support of an online community.

3.C.1.b. Smoking Cessation Trials among PLWH. Dr. Stanton co-authored the results of the first full-scale NIH-funded clinical trial (R01DA12344-06) for smoking cessation among PLWH (N=444). This study compared a motivational enhancement intervention to brief advice. All participants were provided NRT. Using intent-to-treat analyses, 7-day ppa rates ranged from 9-12% at the 2, 4, and 6 month time-points with no differences between

groups.[23] Subsequent analyses led by Dr. Stanton identified key elements across interventions that mediated successful abstinence in the overall sample.[33] At 6 months, abstinence rates improved significantly with increases in psychosocial factors (i.e., changes in self-efficacy); these mediators eliminated the association of NRT use with smoking abstinence, meeting criteria for complete mediation.[33] A more recently funded R01 across 9 clinics in the Northeast tested a culturally tailored cessation intervention for Latinos living with HIV/AIDS (5R01DA018079; PI, Stanton; Co-I, Shuter) that yielded similar 7-day ppa rates (8-11% at 6 months; 6-7% at 12 months). However, significant reductions in cigarettes consumed per day were reported.[32] Latino smokers born outside the US were significantly more likely to be abstinent at 6 months compared to those born in the US, who tended to be daily heavy smokers with a preference for mentholated cigarettes.[81,82]

3.C.1.c. Efficacy of the PSF clinic-based cessation intervention among PLWH (R21DA023362; PI, Shuter). This RCT tested a clinic-based, group intervention (PSF) for PLWH smokers in comparison to standard care (SC).[21] Both conditions included nicotine replacement therapy (NRT). 147 subjects were recruited over 12 months in 2009-2010. Recruitment goals were met, and 96% completed the study. At 3 months, biochemically confirmed 7-day ppa was 19.2% in PSF vs. 9.7% in SC. **Higher loneliness score was an independent predictor of treatment failure**. Session attendance was a challenge, with mean attendance of 4 of 8 sessions. Abstinence rates were significantly higher among those who completed ≥7 sessions (42.9%). Reasons for non-attendance included difficulty traveling to group sessions, feeling sick, conflicts with other appointments, problems at home, forgetting about sessions, and lack of interest. **Many of these challenges would have been mitigated by Internet access to cessation treatment.**

3.C.1.d. Technology access and use among PLWH. In 2009, an Internet use survey administered to 208 PLWH in the MMC ID Clinic[46] reported 56% and 51% of participants had home access to computer and Internet, respectively. In 2010-2011, a clinic survey among 492 PLWH reported 66% had home access to the Internet.[47] As part of our PSFW R21 feasibility study **(3.C.1.e.)** conducted from 2012-2013, of the 178 participants who were referred and screened in the MMC ID Clinic, 97% reported daily home access to the Internet. Among those who participated in the pilot trial, 70% endorsed looking for health or medical information on the Internet, 79% visited a social networking site (e.g., Facebook), 49% looked on the Internet for information or support for people living with HIV, and 81% had access to the Internet on their cellphone. Participants in the pilot trial were given a choice to receive text message reminders about coming back to the program in addition to reminder calls and 74% elected to receive texts. Participants were asked what features of a web-based program they thought would be most helpful: **87% reported that a chat room or social networking on the site with other smokers trying to quit would be helpful**, 83% thought text message reminders about program content would be helpful, and 94% reported phone calls and emails would be helpful reminders to revisit the site. These data strongly dispute the presence of a "digital divide." Our racial/ethnic minority, low SES sample was eager to use a web-based resource to quit, had consistent access to the Internet, and overwhelmingly endorsed the idea of an online community within the program.

3.C.1.e. Efficacy of Positively Smoke Free on the Web among PLWH smokers (Shuter/Stanton MPIs, R21CA163100-01). This recently published[14] NCI-funded pilot RCT tested a static web-based intervention (PSFW) derived from the content of PSF (3.C.1.c.) compared to SC.[14] 138 subjects were accrued over 13 months (100% of target) and 97% completed the study. At 3 months, biochemically confirmed 7-day ppa was 10.1% among PSFW subjects vs. 4.3% of SC. Of the 8 program sessions, mean number completed was 5.5 sessions, and 40% logged into all 8 sessions (compared to 7% who attended all 8 of the in-person group sessions of the PSF program). 18% of those who logged into all 8 sessions and 31% of the women who completed all 8 sessions were abstinent at 3 months. This promising success rate for women highlights the importance of examining subgroup differences in engagement and efficacy as outlined in our exploratory aim. The adherence protocol was critical: all participants received email reminders to return to the website, and over 94% required at least one reminder phone call from study staff who monitored website utilization throughout the study. Over 78% of participants surveyed post-intervention indicated that the PSFW experience was positive in terms of being helpful, meeting expectations, leading to user satisfaction, and being personally relevant; 95.2% indicated that they would recommend PSFW to family or friends who were interested in quitting. In sum, these results demonstrate Internet access (97%), study feasibility (recruited 100% target on-time), adherence (almost half completed all 8 sessions with mean of 5.5 sessions), efficacy (3 month abstinence was 2.3 times higher in PSFW compared to SC), and satisfaction (95% would refer a friend).

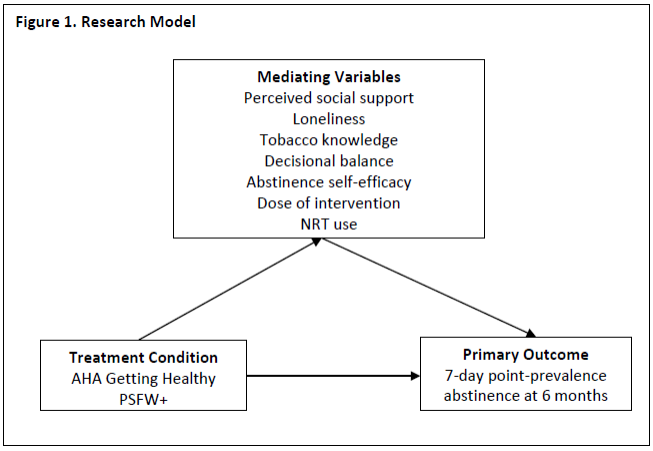
3.C.1.f. Loneliness as central challenge for PLWH smokers.[22] Post-hoc analyses were performed on a combined sample (N=272) from the two R21 (PSF & PSFW) trials listed above to explore loneliness in PLWH smokers[22]: 63% scored above normal range on a validated loneliness scale,[83] and 19% met criteria for extreme

loneliness. Loneliness was associated with lack of a life partner, alcohol use, depression, anxiety, and lower educational level. Those who were abstinent at 3 months had lower loneliness scores at baseline than those still smoking (P=0.09). Loneliness decreased significantly over time among those in the live, group therapy condition, but no changes in loneliness were observed among those in the static PSFW intervention. [[**These findings suggest that the static website failed to reach its full potential due to the absence of a social component, and they provide further justification for the enhancements that we propose in this submission.**]]

3.C.1.g. PSFW+. [[In early 2014, Legacy's software development team adapted the original code base from PSFW **(3.C.1.e.)** and updated it to accommodate security enhancements, feature additions, and a legally-reviewed privacy statement. Online community capabilities were integrated using Vanilla Forums, an open source platform. Integration of this component included adding navigation links to and from the community from the static content, and enabling single sign-on for a seamless transition between the community and static content. We also "skinned" the Vanilla Forums community to maintain the same look and feel as PSFW in order to complete its integration into the intervention. "Seed users" are critical to launching an online community: they create content and respond to posts by others to circumvent the "empty room" phenomenon which is the downfall of many communities.[25,27] In addition, their attitudes and actions set an example for new members to follow and begin to establish community roles and norms.[26] Both current and former smokers with regular Internet access were recruited to serve as seed users. In the summer of 2014, a diverse group of 11 PLWH (8 men, 6 African American, 5 Latino) recruited from the MMC ID Clinic completed an orientation to the PSFW+ site and began actively participating in the nascent community. We piloted PSFW+ to gain experience recruiting and training a quorum of seed users and testing the functionality of the community prototype. All users in this pilot visited the site and posted regularly, and numerous online discussions ensued pertaining to smoking and quitting among PLWH. If funded, the team will begin the study with this core software infrastructure to support the online community, a successful recruitment and training protocol, and a complement of seed users already trained and known to Legacy.]] Expansion of community functions, recruitment of additional seed users, and promotion of the website are planned as part of a comprehensive strategy during the start-up phase to ensure a functional community by trial launch. [[To ensure the ongoing growth and vibrancy of the social network, we have allocated significant funding throughout the grant ($14K/year) to support the efforts of a critical mass of seed users.]]

Summary of Prior Work: These preliminary studies demonstrate the ability of the investigative team to recruit and retain subjects from a large population of PLWH smokers; conduct prospective, real-world, web-based smoking cessation trials; adapt and optimize traditional interventions to modern, innovative technology-based platforms; and participate in intra- and extra-institutional collaborations to accomplish project goals.

3.C.2. Overall Strategy. This is a randomized, controlled trial that will test the efficacy of PSFW+ compared to an attention-matched control in achieving 7-day ppa at 6 months post-randomization in a cohort of PLWH smokers (N=550). Assessments will occur at baseline, 1-, 3-, and 6-months post-randomization with biochemically-confirmed, 7-day ppa at 6 months as the primary outcome **(Figure 1)**. Secondary outcomes include quit attempts, smoking rate, changes in motivation, other metrics of abstinence (e.g., 30-day ppa), and estimated incremental cost per quit. All participants will be offered a full course of NRT and its use will be monitored at each assessment.



3.C.3. Design Considerations

In web-based clinical trials, selection of a suitable control condition is a complex design issue that has both pragmatic and ethical dimensions.[84] [[After careful consideration and in response to prior reviews, we have concluded that comparison of PSFW+ to an attention-placebo will allow us to demonstrate scientifically persuasive results within the framework of a fully-powered efficacy trial conducted against the backdrop of an urgent public health need. RCTs comparing web-based tobacco treatments (in other populations) to attention placebos maximize the demonstrated effect sizes of the experimental interventions according to one meta-analysis.[85] Using a general health-promotion website as an attention control is a standard approach to study design in targeted web-health trials.[86,87] We selected the AHA Getting Healthy program for 2

primary reasons: 1) it contains subject material of relevance to our largely middle-aged population of smokers with at least one cardiac risk factor (i.e. tobacco use) who will participate in the trial; and 2) it consists of a similar number of modules (seven) to PSFW+, and although one module addresses tobacco use, this is not a central theme of the site (we will assess the use of the module and control for it in analyses).]]

3.C.4. Methodology

3.C.4.a. Study Setting. The study will be conducted at two sites: Montefiore Medical Center (MMC) in New York, and MedStar Georgetown University Hospital (MGUH) in Washington, DC. MMC is the main teaching hospital for the Albert Einstein College of Medicine. The **MMC Infectious Diseases (ID) Clinic** in the Bronx, NY provides care to over 3000 PLWH, making it the largest individual HIV care site in New York. MMC also has 10 Comprehensive Health Care Center (CHCC) sites throughout the Bronx that provide HIV care to approximately 850 additional PLWH. MMC is a leader in the field of tobacco use in PLWH, having published some of the earliest work on the relationship between smoking, HAART non-adherence,[88,89] and inferior virologic outcomes,[90] as well as one of the most detailed views of the sociobehavioral profiles of PLWH smokers.[39] MMC has participated in four NIH-funded tobacco treatment trials for PLWH and has distinguished itself in the areas of recruitment and retention (**3.C.1.c.** and **3.C.1.e.**). The three trials that have been completed to date met accrual targets on-time and on-budget with an overall loss to follow-up of <5%. The **MedStar Georgetown University Hospital (MGUH) HIV Clinical Program** is one of the largest providers of comprehensive HIV care in Washington, DC, the city with the highest HIV prevalence in the nation. MGUH provides comprehensive HIV care to approximately 1200 PLWH, of whom 30% are women and 65% are African American. MGUH has a long track record of participation in multiple large clinical trials including the AIDS Clinical Trials Group, the Women's Interagency HIV Study, and the HIV Prevention Trials Network. All patients benefit from the medical home created within MGUH with access to a social worker, adherence specialist, nutritionist, and case manager. Patient retention within the clinic is 95% and the retention rate across various clinical trials has exceeded 95%.

Conducting the trial at these two clinical sites strengthens the proposal in several ways: 1) it expands the overall PLWH recruitment pool; 2) it increases the geographic and racial/ethnic diversity of the study sample since the Bronx site is predominantly Latino, and the DC site is predominantly African American; 3) it adds the considerable expertise of physicians at each site as co-investigators; and 4) it leverages the affiliation that Georgetown has with the American Legacy Foundation. Both MMC and MGUH have active Consumer Advisory Boards (CABs) who represent the needs of clinic patients in routine care and in research.

3.C.4.b. Subjects. We will recruit N=550 adult PLWH smokers. ***Inclusion criteria are***: 1) age 18 or older; 2) current smoking as defined by a validated tobacco use measure;[91] 3) laboratory confirmed HIV-infection; 4) receipt of care at either MMC or MGUH study site; 5) English language fluency [[(a language criterion was established given concerns regarding the ability to maintain a Spanish language online community and the necessarily different online experience that a second language would engender. Less than 10% of the Latino population of the MMC ID Clinic is monolingual Spanish-speaking)]]; 6) motivation to quit within the next 30 days; 7) at least weekly Internet and email access;[92] and 8) REALM literacy score of 19/66 or above, indicating reading level of at least 4-6 grade[61] (PSFW content was written for this literacy level). ***Exclusion criteria are***: 1) previous participation in any trial of Positively Smoke Free interventions or use of PSFW+; 2) pregnancy; 3) contraindication to NRT; and 4) current participation in other cessation treatments. PSFW+ seed users will be excluded. To avoid study condition contamination and to maintain the statistical independence of outcomes, otherwise eligible individuals who are spouses, partners, and/or roommates of study participants will be excluded. All ineligible patients will receive a Positively Smoke Free smoking cessation brochure and will be encouraged to access nationally-available (free) quitline counseling.

3.C.4.c. Recruitment Approach. Participants will be referred by primary care providers at the MMC ID Clinic and the MGUH ID Clinic. Approximately 65% of MMC ID Clinic patients are smokers representing a pool of ~1950 smokers; the MGUH ID Clinic serves an estimated 1200 patients/year, representing a pool of ~780 estimated smokers. These are underestimates since over 500 new PLWH patients enter these care systems annually. Recruitment into the trial will begin in the 4th quarter of Year 1 and will continue for 38 months. Across all sites, we aim to enroll 14.5 subjects/month (7-8/month MGUH; 6-7/month MMC [the lower recruitment target at MMC is in consideration of a concurrent RCT at that site]). Study staff will be on-site full-time at each location throughout the project to enroll participants who are referred by their primary care providers. In our previous PSFW R21 study **(3.C.1.e.)**, conducted at a single site, we recruited N=138 smokers over 13 months (10.6 per month) using the same primary care provider referral strategy. Thus, our target of N=550 over 38 months (14.5/month) should be attainable. In the event we do not meet accrual goals, research staff will directly recruit patients in clinic waiting areas.

3.C.4.d. Study Enrollment and Randomization. Following referral from primary care providers, research staff will conduct eligibility screening and informed consent. Consented participants will be randomized to one of the two study conditions. Based on predictors of smoking behaviors that emerged in our prior work,[21,23] randomization will be stratified by gender and education level within each clinic. An online random plan generator (http://www.randomization.com) will be used to create an allocation schedule. The schedule will be fully documented with the reference citation of the pseudo-random number generator, the seed used to start the generation process, the number of study conditions (2), the allocation ratio (1:1), and a copy of the assignment list.

3.C.4.e. Interventions. All subjects will be offered a 3-month supply of NRT at the enrollment visit. Subjects will be provided an actual supply of nicotine patches or a prescription which can be filled on site (for subjects with insurance coverage). We will encourage study-provided patch use only during the trial.

[**Control Condition: American Heart Association Getting Healthy web-program**

Getting Healthy is a 7-module website with interactive features aimed at reducing cardiovascular risk through healthier lifestyle choices. Modules are: Nutrition Center, Physical Activity, Healthier Kids, Weight Management, Stress Management, Quit Smoking, and Workplace Wellness. Each of the modules has a separate URL. Participants can sign up for a monthly e-newsletter. Getting Healthy does not have its own dedicated online community. We will e-mail a link to a new module weekly in order to parallel the seven weeks of PSFW+ sessions, and will send two email reminders and one text (if the subject agrees to receive text messages) weekly to prompt users to visit the module, as well as a reminder phone call after 10 days of non-use to parallel the adherence protocol in the PSFW+ condition. We estimate that each module will take an average reader 15-30 minutes to complete which corresponds closely to the time requirement for PSFW+ written content. Legacy will create a "portal page" that will require control participants to log in, generating data regarding website use. At the time of enrollment, the research assistant will introduce the participant to the portal page. Following entry of a unique username and password that will be assigned during enrollment, participants will be routed to the Getting Healthy module of the week. This approach will optimize attention matching and will also allow the team to collect basic Getting Healthy utilization metrics.]]

PSFW+: Positively Smoke Free on the Web plus Online Social Network PSFW+ participants will be registered on the website by the research assistants following randomization. Each participant's unique Study ID will be tied to his/her website registration to enable linkage of website utilization metrics with other data collected during the trial. Registration involves creating a username and password, entering an email address, and a mobile phone number (if available). The participant will receive a confirmation email following registration that contains a link to the site and instructions to bookmark it in his/her Internet browser for easy access.

PSFW+ Core content: An overview of PSFW content is in **Table 1**. With input from PLWH smokers, HIV specialists, psychologists, graphic artists, and software engineers, we distilled the content of the PSF social-behavioral group counseling curriculum[21] into a web intervention. The course content has gone through multiple rounds of revision based on input from PLWH smokers, experts in HIV and smoking cessation, the MMC ID Clinic CAB, multiple pilot trials and usability testing. Themes of relevance to PLWH smokers permeate the content. The heterogeneity of the PLWH community and how this relates to smoking behaviors (i.e., similarities and differences between drug users, LGBT, and depressed individuals) is highlighted. "Microtargeting" of subsets of PLWH (e.g., LGBT) has consistently received the praise of participants in our pilot work. Consistent with

Table 1. An overview of Positively Smoke Free on the Web (PSFW) and Getting Healthy content.

Positively Smoke Free			Getting Healthy
Week	**General Themes**	**HIV-Referent Themes**	**Module Title**
1	– Education about tobacco use – Role of social and buddy support – Setting quit date	– Tobacco related risks in PLWH – Myths about smoking benefits for PLWH	– Nutrition Center
2	– Social cues of smoking and coping strategies – Behavioral tools to resist craving – Role of pharmacotherapy	– Self-discipline, instant gratification, and improved health outcomes for PLWH	– Stress Management
3	– Cessation as an element of a healthy lifestyle	– Healthy lifestyle decisions in PLWH	– Physical Activity
4	– High risk situations – Coping with slip-ups	– Comparison to high risk situations pertaining to HIV – Comparison of tobacco slip-ups to HAART slip-ups	– Healthier Kids
5	– Quit Day: pharmacotherapy, social support, coping w high risk situations and slips	– Quit day compared to start of HAART day – Enduring temporary discomfort for the sake of long-term health	– Weight Management
5.5	– Coping with urges to smoke – Assertiveness training	– Urges to skip HIV-medications or appointments – Assertiveness in HIV-care	
6	– Thoughts that lead to relapse – Maintaining abstinence	– HIV, pain, tobacco use, and smoking cessation	– Quit Smoking
7	– Long-term health benefits of cessation – Planning for long-term abstinence	– Abstinence as a major element of long-term health in PLWH – HIV as a chronic disease	– Workplace Wellness

Social Cognitive Theory,[93] content focuses on providing information, increasing motivation to quit, and increasing self-efficacy to resist smoking temptations (**Table 2**) via presentation of objective data as well as hypothetical "real world" scenarios of particular relevance to PLWH smokers. Users are given tools and options to cope with smoking urges. NRT use is encouraged. **Online social network:** The PSFW+ community runs on open source forum software by Vanilla Forums. We created a full-featured discussion forum with unlimited categories and user profiles that is customized to look like the main site. Vanilla Forums enables single sign-on for a seamless experience between the static content and online community. PSFW+ users can create a user profile with a unique avatar or personal photo, and can create a profile "wall" on which other users may post comments, images, or video. The primary interface is a feed of discussion threads: users create discussions or polls, and other users may post comments to the discussion or answer the poll. Users can also exchange private messages. The **PSFW+ Community Guidelines** emphasize the importance of creating and maintaining a safe environment for people to exchange information and support. The guidelines also remind users that all content posted in the community is publicly available, and that the administrator may remove messages that are spam or solicitations. Users who persistently violate Community Guidelines will have their community profile removed from the site. Our experience with several online communities with thousands of users is that these occurrences are infrequent; should they occur during the study period, we will account for this in our analyses. Involvement of an experienced administrator is integral to managing these situations proactively to ensure the smooth operation and success of an online community,[24,94] especially during its nascent phase. The **PSFW+ Community Administrator** will monitor all public discussions and comments on the community, encourage interactions between community members, review all reports of inappropriate content that do not follow the Community Guidelines (such as spam), and serve as the main liaison between technical staff and community members for any technical issues. The **PSFW+ Terms of Use** and **Privacy Policy** make explicit that all content posted in the community is publicly available information and users are legally responsible for any content they post on the site. The registration page states "By clicking Submit, I agree to the Positively Smoke Free Terms of Use and Privacy Policy" (available via hyperlink). The treatment of the unique privacy concerns of a PLWH online community and its attendant legal implications have been carefully considered and are discussed in detail in the Human Subjects section.

A critical mass of 10 or more seed users will be retained on contract to ensure that active dialogue within the community is maintained. Seed users will be responsible for posting daily on at least 15 days a month, starting new discussions, and responding to posts in existing ones. As PSFW+ enters the public domain, we will promote the site nationally to PLWH smokers through posts on a variety of HIV/AIDS social support groups and related non-profits on social networking sites, and outreach to a national health communications listserv.

PSFW+ Adherence Strategies: Intervention adherence is critical to maximizing the efficacy of Internet cessation interventions. Poor adherence to eHealth interventions has been documented across health behaviors, websites, and study populations.[78,95-115] Our outcome findings in the PSFW pilot **(3.C.1.e.)** substantiate the importance of adherence in achieving abstinence. Building on Dr. Graham's extensive experience in this area[116] we will implement intensive, multicomponent strategies to maximize adherence to PSFW+ and examine website utilization as a predictor of abstinence. Our approach mimics a face-to-face treatment paradigm in which participants are given feedback about their treatment progress, reminded about intervention features/content they have not yet accessed, and encouraged to remain engaged in treatment. This kind of "dialogue support" (e.g., reminders, suggestions, praise) is one of the strongest predictors of website adherence.[117] Building on evidence that supports the effectiveness of email[109,118,119] and text messages[120-128] in improving treatment adherence, we will develop automated, personalized prompts and reminders that are tailored real-time to an individual user's interaction with PSFW+. [[Similar to the control condition, users will be encouraged to login to a new session approximately once per week (twice during quit week), and reminder emails and texts will reinforce this schedule. They will be permitted to access the online community ad libitum.]] Email messages will be delivered after 7 consecutive days of site non-use; a text message will also be sent if the email does not precipitate a return visit to the site within 2 days. As in our PSFW R21, clinic staff will contact participants by phone after a period of 10 days of non-use. For participants who remain active on the site, weekly email and text messages will encourage ongoing use of all features on the site, including community participation for up to 8 weeks. Participants can reply STOP to the text messages at any time. We will track all adherence-promoting activities for analyses.

3.C.5. Data Collection and Measures

Assessments will be conducted via in-person interviews with biologic samples (exhaled carbon monoxide) in the respective clinic at baseline, 1, 3, and 6 months post-randomization. Self-report measures will be administered via Audio Computer-Assisted Self-Interview (ACASI). Study staff will assist with the ACASI interface as needed. Study measures described below are standard instruments commonly used in cessation treatment studies. If participants are unable to come to the centers to complete the ACASI, they may be completed over the telephone with the assistance of study staff. The relationship of the selected measures to the intervention's behavioral model is summarized in **Table 2**.

Table 2. PSFW Intervention Components by Social Cognitive Theory (SCT) Principles

SCT Principles	Generic intervention components	Tailored intervention components	Measures
Enhancing knowledge	– Biobehavioral aspects of smoking & nicotine addiction – Role of pharmacotherapy	– Dangers of smoking in PLWH – Myths about benefits of smoking in PLWH are explored/dispelled	– Adult Use of Tobacco Survey (knowledge questions) – Perceived Risks and Benefits Questionnaire (PRBQ)
Observational learning	– Multiple real-life vignettes	– Vignettes discuss feelings and actions of PLWH smokers trying to quit – Vignettes microtarget PLWH subgroups	– Decisional Balance Short Form
Building self-efficacy	– Information about quitting and pharmacotherapy – Responding to urges, slip-ups, and relapses – Enlisting social support – Assertiveness training	– Past successes w HIV-related challenges (mastering HAART, confronting other addictions) emphasized as behavioral paradigms – Responses to cessation slip-ups compared to HAART slip-ups – Strategies to manage psychiatric symptoms during quitting	– Self-Efficacy/Temptations Scale – Partner Interaction Questionnaire – UCLA Loneliness Scale – CES-D (depression) – State/Trait Anxiety Scale (anxiety)
Outcome expectations ***Short term*** ***Long term***	– Improvement in respiratory status – Monetary savings – Urges/cravings for cigs – Weight gain – Enhanced health/ longevity	– Possible worsening of depression/anxiety – Weight gain (desirable outcome for many PLWH) – Better long-term CD4+, VL, and survival	– Perceived Risks and Benefits Questionnaire – CES-D – State-Trait Anxiety Scale

Tobacco Use (Aim 1 measures): Self-reported 7-day ppa will be measured at each follow-up and biochemically verified by exhaled carbon monoxide (ECO) at each study visit. Staff will be trained in the use, maintenance, and calibration of the Bedfont piCO+ Smokerlyzer. An ECO measurement of <10 ppm will be considered abstinent and of ≥10 ppm non-abstinent.[23] Discordant self-report and ECO data because of marijuana effects on ECO will be clarified with saliva cotinine strips.[129] Secondary outcomes include standardized items from the CDC Question Inventory on Tobacco (CDC-QIT)[91] including number of quit attempts, continuous abstinence, and 30-day ppa. Daily cigarette and other tobacco consumption and age at initiation will be assessed. Nicotine addiction will be measured with the Fagerström Tolerance Questionnaire,[130] and the Contemplation Ladder will measure readiness to quit.[131]

Proposed Mediators (Aim 2 measures): Perceived social support will be measured with the Multidimensional Scale of Perceived Social Support to assess perceived general support arising from family, friends, and significant others.[80,132,133] Smoking-specific social support will be measured with an adapted version of the Partner Interaction Questionnaire.[19] The UCLA Loneliness Scale[83] will measure subjective feelings of loneliness or social isolation. Dr. Graham's Online Social Support Scale for Smokers (OS4)[134] – will be adapted to assess dimensions of perceived support from the PSFW+ online community.

Potential Moderators and Mediators (Exploratory Aim): Potential **moderators** include demographic variables (age, gender, race, ethnicity), clinical variables (e.g. HIV risk behavior, most recent CD4+ and viral load, histories of cardiovascular, pulmonary, neoplastic disease, and substance use assessed with the NIH/NIAID Baseline Substance Use Self-Report),[135] depression (Center for Epidemiologic Studies Depression Scale),[136] and anxiety (State-Trait Anxiety Scale).[137] Potential **mediators** include: 1) tobacco knowledge measured using standardized items from the Adult Use of Tobacco Survey;[91] 2) self-efficacy measured with the Self-Efficacy/Temptation Scale;[138] 3) Smoking Decisional Balance (Short Form);[139] 4) risks and benefits of smoking measured with the Perceived Risks/Benefits Questionnaire,[140] modified to include HIV-referent questions (e.g. "Does smoking raise/lower your CD4+ count?"); 5) PSFW+ and attention-placebo utilization metrics as described in the next section; and 6) use of NRT and other quit methods. NRT use will be assessed with the 4-item Morisky Scale;[141] side effects,[142] dosage, duration of use, pattern of use ("on and off" vs. "everyday"), and continued smoking while using NRT will be assessed.

Additional Control and Evaluation Measures: Other treatment exposure: Using standard assessment items administered in previous trials,[143] we will assess use of other cessation treatments including alternative smoking cessation websites, non-study NRT, prescription medications (e.g.varenicline), behavioral treatments (pamphlet/book, live and/or telephone counseling), and alternative quit methods (e.g., acupuncture, hypnosis). Individuals who report use of cessation websites will be asked to identify each specific website and the number of visits. [[Information about membership in any other health-promoting or tobacco treatment online communities will be collected from all subjects.]] **Treatment Satisfaction Questionnaire**: PSFW+ participants will be asked the number of times they visited the website, the approximate length of each visit, and ratings of overall satisfaction and perceived helpfulness of the site. Participants who report that they did not visit the website will be asked for specific reasons for non-use (e.g., lost Internet access, lack of interest, etc.). Similar questions will be asked regarding the Getting Healthy website. Additional questions will address knowledge of and familiarity with PSFW+ and Getting Healthy; these questions will be designed to detect potential study contamination. **PSFW+ Utilization Metrics**: We will extract the following utilization variables: date/time of registration, # site visits, date/time of each visit, # page views, date/time of each page view, # page views per session, # interactive component clicks, changes to personal profile (e.g., email, username), whether the user signed up for text messages, # text messages sent, and # emails sent to participant from the system. We will also extract the following variables from the Vanilla Forums database specific to community utilization: # clicks through to the community from PSFW+ content pages, # direct visits to the community, # discussion posts, # comments, # private messages sent/received, # wall posts made/received, and whether or not they customized their profile (e.g., photo). Getting Healthy utilization metrics will rely on data collected from the portal page (3.C.4.e.) and subjects' historical recall. At the end of Visit 2, we will administer the 18-item Sense of Virtual Community scale to PSFW+ participants.

[[In order to calculate the incremental cost per quit, we will compile the costs of website hosting and maintenance, payments to the community administrator and seed users, staff support required to make reminder phone calls, and receipts for nicotine patches. Research costs and development costs for PSFW+ and the portal page for the Control condition will not be included.]]

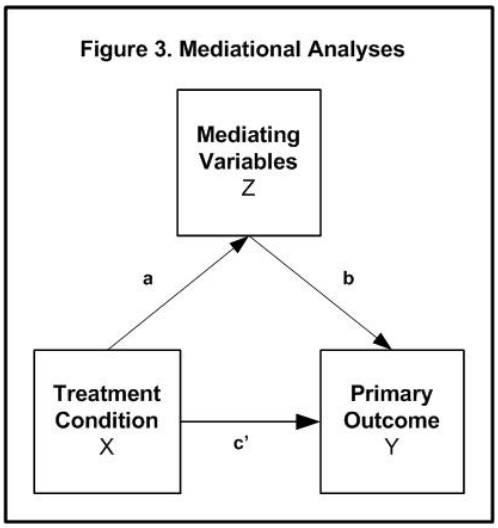
3.C.6. Data Analysis Plan and Sample Size Calculations

3.C.6.a. Preliminary Analyses. We will calculate descriptive statistics and perform bivariate analyses using t-tests (or nonparametric tests if needed), Chi Square tests (or Fisher's exact tests if needed), and Pearson (or Spearman) correlation coefficients to evaluate relationships among baseline measures (e.g., demographic characteristics), mediating variables (e.g., perceived social support) and outcome measures (7-day ppa). Due to randomization, we expect the two treatment groups to be balanced with respect to the baseline measures. However, baseline measures identified in bivariate analyses as statistically significantly (at the 0.05 level) associated with the outcome measures will be included in the corresponding regression models as covariates to increase statistical power.

3.C.6.b. Specific Aim 1: Outcome Analyses. The primary outcome is 7-day ppa at 6-months.[144] The primary study analyses will adopt an intent-to-treat (ITT) strategy; secondary complete-case, as-treated analyses, and analyses that evaluate the role of treatment intensity (i.e., "dose") will also be conducted. In ITT analyses, the association between treatment group and 7-day ppa at 6-months will be evaluated using a logistic regression model that will have abstinence as the binary outcome, treatment groups as the main predictor, and covariates identified in preliminary bivariate analyses. Subjects who fail to return for the 6-month visit, decline ECO testing, or have discrepant abstinence and ECO results (that cannot be clarified with saliva cotinine strips) will be considered non-abstinent. This is a standard primary outcome when measuring the efficacy of a smoking cessation intervention in a definitive trial.[21,144] It will be defined as a negative response to the validated question *Have you smoked cigarettes (even a puff) in the last 7 days, including today?*[91] combined with an ECO level <10 ppm (or negative salivary cotinine when applicable).[23] Additional measures of abstinence or tobacco usage reduction will be similarly examined for association with treatment group in secondary analyses.[91] Abstinence data will be collected at 1 and 3 months to assess the correlation between time points. [[A formal cost-effectiveness analysis that includes detailed accounting of effects on health-care utilization over time is beyond the scope of the project. However, we will calculate incremental cost per quit using our abstinence data and the economic metrics listed in 3.C.5. This is a standard cost-effectiveness metric for tobacco treatments,[145] and it will be calculated with bootstrap 95% confidence intervals to provide a starting point for discussions about the cost-economics of tobacco treatment in this population. This outcome is bound to overestimate the ultimate cost of a widely-disseminated intervention, because web-based programs of this sort are scalable at low expense.]]

Missing data. We expect less than 10% missing data at any time. Under an intention-to-treat approach, participants who had been considered non-smokers up to the point of losing contact will be considered relapsers at future data points. Multiple imputation methods[146] will be used to deal with missing data, assuming a missing at random (MAR) mechanism; we will generate 10 multiple imputed datasets, analyze each dataset separately, and then combine the results across the 10 datasets using Rubin's method.

3.C.6.c. Specific Aim 2: Mediator Analyses. Aim 2 hypothesizes that greater social support mediates the intervention-cessation relationship. Figure 3 depicts our mediational model: **X** represents treatment group, **Z** represents the hypothesized mediator (e.g., perceived social support), **Y** represents outcome (7-day ppa), ***a*** is the regression path between treatment group and mediator, ***b*** is the regression path between mediator and outcome, and ***c'*** is the regression path between treatment group and outcome controlling for the effect of the mediator. The 3-month assessment will be used for mediator **Z** and the 6-month measure of 7-day ppa will be used as the primary binary outcome **Y**. To increase statistical power of our mediation analysis we will use the product of coefficients method.[147] We will estimate the coefficient ***a*** by fitting a linear regression model with the putative mediator as the continuous outcome, treatment arm as the main predictor, and covariates identified in bivariate analyses as being associated with social support. We will estimate the coefficient ***b*** by using a logistic regression model with abstinence as the binary outcome, **Z** as the main predictor, and covariates identified in bivariate analyses as being associated with abstinence. We will then calculate the mediated effect as the corresponding product of these coefficients with standard error and 95% confidence interval estimated according to MacKinnon.[148] Since the sampling distribution of this product shows considerable skewness and kurtosis, interval estimation will be based upon bias-corrected and accelerated (BCA) bootstrap confidence intervals.[149] Potential mediators in Figure 1 will be analyzed separately, and additional analyses will be conducted to evaluate interaction effects.



3.C.6.d. Exploratory Aim: Moderator Analyses. We will examine potential moderators of the intervention-smoking cessation relationship (e.g., demographics, depression, anxiety). Effect modification analyses will be conducted by testing interaction terms between treatment group and selected variables. Interaction terms will be added to variables already in the regression models (3.C.6.b.). Subsequent stratified analyses will be performed to explore specific moderation effects. **Mediator Analyses.** Exploratory mediation analyses will follow the approach in 3.C.6.c.

[[**3.C.6.e. Sample Size Considerations: Aim 1.** Using the mean abstinence rates in the SC arms in our two recent R21 trials (9.7%[21] and 4.3%[14]), and up-adjusting the rate slightly in consideration of the attention-placebo, we estimate a 7-day ppa at 6 months in the control condition will be 7.5%. Our estimate of the efficacy of PSFW+ is based on research by our team[20] and others[62] who have demonstrated that visits to an online community increase abstinence rates. In the BecomeAnEX outcome evaluation,[20] 7-day ppa at 6 months ranged from 11.1% (ITT) to 20.7% (responder only); individuals who visited the online community two or more times were more than twice as likely to be abstinent than those who never visited (OR=2.22, 95% CI 1.34-3.69, P=.002) controlling for a broad range of demographic, smoking, and psychosocial covariates. These results are consistent with An et al.[62] who reported a near doubling of abstinence rates (OR=1.91) among individuals who used individual messaging in an online cessation program. The benefits of an online community are not simply for the minority who actively post; reading communications ("lurking") also has beneficial effects.[150,151] Therefore, we estimate that PSFW+ combined with our intensive adherence strategies to promote engagement and utilization will increase abstinence rates by 2.05 times over control, yielding a 6-month quit rate of 15.4%. This estimate is deliberately conservative in that we have chosen to use as the base rate our estimate of control (7.5%) rather than the quit rate from our previous trial of PSFW (10.1%). This will ensure that we are adequately powered to detect treatment group differences between PSFW+ and control. Assuming abstinence rates of 15.4% and 7.5% in the PSFW+ and control conditions, respectively, 254 subjects in each arm will be necessary to achieve power of 0.8 with an alpha=0.05. Projecting a liberal 9.2% loss-to-follow-up based on our previous NIH-funded trials (R21CA163100-01, R21DA023362), we will randomize N=275 per arm.]]

Sample Size Considerations: Aim 2. We are able to detect a mediation effect (coefficient product) of small size

(with coefficient product parameters a=0.14, b=0.14) with at least 80% power for each mediator given our expected sample size of N=508 at 6 months.[152]

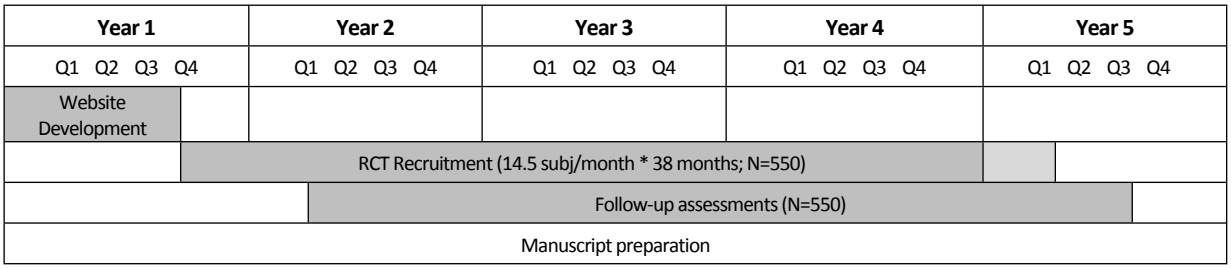
3.C.7. Potential Problems and Solutions

Subject Attrition. Loss to follow-up will be minimized through the use of standard tracking/contact sheets, reminder calls/emails/texts, incentives linked to follow-up completion ($30 cash each visit), and provision of travel fare for all study visits. We will emphasize that incentives are not dependent on website usage or on abstinence, but rather on completion of study visits. Retention rates have been high in our previous clinical trials: during 7 years of participation in Community Programs for Clinical Research on AIDS (CPCRA) trials, MMC ranked in the top 3 sites nationally for retention, losing <2% of subjects from long-term follow-up. Retention rate within various clinical trials (e.g., ACTG, WIHS, HPTN) at MGUH are also impressively high (98%). The aggregate loss to follow-up rate in the three tobacco treatment RCTs conducted in the MMC ID Clinic has been 4.8%.

Study Condition Contamination. To prevent contamination (i.e., subjects accessing non-assigned study websites), we will record control participants' email address at the time of study enrollment in a database linked to the PSFW+ data store. Control participants who attempt to register on PSFW+ using a recorded email address will be redirected to the welcome page of the Getting Healthy site. It is also conceivable that control subjects will register on PSFW+ with a different email address. We will probe for this occurrence and for PLWH+ utilization of the Getting Healthy website in the Treatment Satisfaction Questionnaire at follow-up and will adjust the analyses accordingly.

Generalizability. Once efficacy is established in this controlled trial with optimal recruitment and in-person assessment protocols, future dissemination studies will be conducted that will prioritize external validity.

3.C.8. Timeline and Benchmarks for Success*:* Months 0-9: Modifications and enhancements to PSFW+ including adherence prompts, technical strategies to minimize contamination, efforts to grow and evaluate online community, refinement of assessment protocols, programming of ACASI systems. **Months 10-54:** Recruitment and follow-up at 1, 3- and 6-months, with the final follow-up in Month 54. Preliminary data analyses will be conducted throughout the project. **Months 55-60:** Final outcome analyses and manuscript preparation.



Benchmarks for success: 1) successful recruitment of overall sample size and racial/ethnic minorities in accordance with targeted enrollment projections, and 2) study completion rate of ≥ 90%. In the unlikely scenario that recruitment lags, research staff will recruit in clinics and extend recruitment until recruitment goals are met. MMC and MGUH both enjoy collegial academic relationships with nearby HIV-care centers caring for thousands of additional PLWH smokers, and these may serve as secondary referral sources if the need to augment recruitment arises. If follow-up rates are <90%, we will implement more intensive follow-up strategies and increase incentives as our budget permits.

5. PROTECTION OF HUMAN SUBJECTS

This Human Subjects Research meets the definition of a clinical trial which will require registration in ClinicalTrials.gov.

5.A. RISKS TO HUMAN SUBJECTS

Human Subjects Involvement, Characteristics, and Design

The MMC ID Clinic population is 43% female, 52% Latino/a, 44% African American/Caribbean, 4% White, non-Latino/a. The patients report various overlapping transmission categories: 48% heterosexual, 16% IDU, 14% same sex contact, and 12% unknown. Approximately 68% of patients have CDC-defined AIDS. Of those who provided household income data (63% overall), 91% were living below the official poverty line. 94% are insured by Medicaid, Medicare, or the Ryan White AIDS Drug Assistance Program (ADAP). Based upon aggregate substance use data

from a random selection of clinic patients (N=204), 65% are current smokers (73% of males and 57% of females, Dr. B. Zingman, personal communication).

MMC ID CLINIC 2013 STATISTICS (estimated summary statistics of clinic flow)*

		Am. Ind.	Asian	Black	Latino/a	White	Other	Total
Adults	Female	5	2	614	644	48	1	1314
	Male	3	7	709	912	76	0	1707
Total		**8**	**9**	**1323**	**1556**	**124**	**1**	**3021**

* Transgender individuals (approximately 1% of the overall population) are included in the gender statistics with which they self-identify.

The MedStar Georgetown University Hospital (MGUH) HIV Clinical Program is one of the largest providers of comprehensive HIV care in Washington, DC, which has the highest HIV prevalence in the nation. The clinic structure is designed to overcome two important barriers which have limited access to care in Washington, DC: 1) uninsured rates above the national average, and 2) poverty levels. MGUH provides comprehensive HIV care to approximately 1,200 HIV infected patients, of whom 30% are women and 65% are African American. MGUH has a long track record of participating in multiple large clinical trials including the AIDS Clinical Trials Group, the Women's Interagency HIV Study, and the HIV Prevention Trials Network. It has an established framework in which patients participate in clinical trials. All patients benefit from the medical home created within MGUH with access to a social worker, treatment adherence specialist, nutritionist, and case manager. Retention rate within the clinic is 95% and retention rate within various clinical trials is 98%.

MedStar/Georgetown ID Clinic (estimated summary statistics of clinic flow)*

		Am. Ind.	Asian	Black	Latino/a	White	Other	Total
Adults	Female	0	7	222	36	89	0	354
	Male	0	17	485	84	223	0	809
Children	Female	0	0	15	0	0	0	15
	Male	0	0	22	0	0	0	22
Total		**0**	**24**	**774**	**120**	**312**	**0**	**1200**

* Transgender individuals (approximately 1% of the overall population) are included in the gender statistics with which they self-identify.

Inclusion Criteria: We will recruit N=550 adult PLWH smokers. Inclusion criteria are: 1) age 18 or older; 2) current smoking as defined by a validated tobacco use measure; 3) laboratory confirmed HIV-infection; 3) receipt of care at either MMC or GUH study site; 4) English language fluency; 5) motivation to quit within the next 30 days; 6) at least weekly Internet and email access; 7) REALM literacy score of 19/66 or above, indicating reading level of at least 4-6 grade (PSFW content was written for this literacy level); and 8) willingness to provide informed consent and undergo randomization.

Exclusion Criteria: 1) previous participation in any trial of Positively Smoke Free interventions or use of PSFW+; 2) pregnancy; 3) contraindication to NRT; and 4) current participation in an active smoking cessation treatment (e.g., group therapy, use of pharmacotherapy). PSFW+ seed users will be excluded. To avoid study condition contamination and to maintain the statistical independence of subject outcomes, otherwise eligible individuals who are

spouses, partners, and/or roommates of study participants will be excluded. All ineligible patients will receive a Positively Smoke Free smoking cessation brochure and will be encouraged to access nationally-available (free) quitline counseling.

Inclusion of Women and Minorities: With the exception of pregnant and nursing women, women will be fully included in the study. The safety of NRT has not been established in pregnant women or women who are breastfeeding. Furthermore, pregnant women smokers should be referred for aggressive smoking cessation interventions with proven efficacy, so allocation to the control condition would conflict with best care practices. The exclusion of women who are breastfeeding is of little practical significance since breastfeeding is contraindicated in HIV-infected women in the US. The vast majority of the aggregate clinic populations belong to ethnic minority groups, and the investigators expect the study cohort to reflect the ethnic makeup of the clinics. Asian and Pacific Islanders and Native Americans will be fully eligible for enrollment but are unlikely to comprise a numerically important subset of the study sample because they make up less than 3% of the clinics' populations.

Inclusion of Children: Clinic patients aged 18 to 20 will be eligible for inclusion in the study. A small number of individuals in this age range typically attend the clinic site each year as they transition from pediatric/adolescent care settings. There were no children in the MMC ID Clinic population in 2013, although a small number are expected to transition from the adolescent clinic in future years. Younger children and adolescents have smoking-associated behaviors and risks that differ from those of the adult population. For younger children, the primary medical concern is exposure to environmental cigarette smoke. Adolescent smokers typically smoke fewer cigarettes than adults, with more irregular patterns of cigarette consumption. Because of these significant behavioral differences, and because they receive care in separate facilities, we will not include younger children or adolescents in the proposed project.

Randomization: Following referral from primary care providers, research staff will conduct eligibility screening and informed consent. Once consented, the participant will be randomized to one of the two study conditions. Based on strong predictors of smoking behaviors that emerged in our prior work, randomization will be stratified by gender and education level within each clinic. An online random plan generator (http://www.randomization.com) will be used to create an allocation schedule. The schedule will be fully documented with the reference citation of the pseudo-random number generator, the seed used to start the generation process, the number of study conditions (2), the allocation ratio (1:1), and a copy of the assignment list.

Collaborating Sites: Cassandra Stanton, PhD (MPI) at Westat will oversee the conduct of the study at Georgetown which is in close proximity to her worksite and with which she maintains an ongoing affiliation. The Georgetown site will recruit participants from the MGUH HIV Clinical Program. Dr. Kumar will be responsible for recruitment and follow-up at this site, and Dr. Stanton will oversee the overall conduct of the study at Georgetown. Montefiore Medical Center (MMC) will recruit patients from the MMC Infectious Diseases (ID) Clinic in the Bronx, NY. Dr. Shuter from MMC will serve as MPI and provide expertise in HIV care and tobacco treatment. Dr. Graham and her software development team at the American Legacy Foundation will be responsible for delivering the PSFW+ intervention. They will be responsible for administering the online community and for developing and monitoring the automated tracking metrics on website utilization.

Sources of Materials

Specimens, Records, or Data: Enrolled subjects will complete measures **(see Table 2)** in a private office using an ACASI interface on a password-protected study computer. Study staff will be nearby to render any assistance necessary. Input data will be maintained on the computer's hard drive and will be uploaded on the day of questionnaire completion via a secure Sharepoint portal to the AECOM Epidemiology Informatics/Study Management Unit (EISMU - please see Protection of Study Data below and the AECOM Resources section). Exhaled carbon monoxide measurements will be performed according to manufacturer's instructions and discordant abstinence data (frequently observed in marijuana users) will be clarified with saliva cotinine strips. Biochemical validation results will be keyed by study staff into the study databases. All locally maintained computer data will be stored on password protected computers/servers and backed up to encrypted Ironkey USB drives.

Website utilization metrics will be extracted from the back end of the PSFW+ intervention. These metrics include 1) an event tracking database within the PSFW+ application for non-community related actions, and 2) community related data from the Vanilla Forums database. From the event tracking database within the PSFW+ application we will extract individual-level metrics utilization including the date/time of each session and page visited, date/time of each site login, the referring URL for each site visit, the date/time of registration, number of clicks through to the community (date/time stamped), number of page views per session (date/time stamped), number of interactive component clicked (date/time stamped), and changes to profile such as email or username. We will also track the number of email and text messages sent to each participant as a function of the individually tailored adherence strategies we will employ for this study. From the Vanilla Forums database, we will extract individual-level tracking metrics including (among others) visits, number of discussions participated in, number of comments made, number of private messages sent/received, number of profile posts made/received, and whether a custom profile photo was uploaded.

For subjects in the control condition, time and duration of each login to Getting Healthy via the portal page will be recorded. Email and text message reminder data will be compiled in the same manner as the PSFW+ condition.

Materials Access: During the course of the project, the Investigators, Data Analyst, Software Development Team, Community Administrator, and Project Manager will have access to individually identifiable information about human subjects. In addition, Vanilla Forums technical and support staff will have access to registration data and any data arising from participation in the online community. This access is detailed in the Vanilla Forums Terms of Service and Privacy Policy which are referenced in the PSFW+ documents. The Getting Healthy website will have access to users' IP addresses, but these users will not be distinguishable from any other user of the AHA Getting Healthy site. These various levels of access will also be listed in the participant informed consent document.

Protection of Study Data: All data in transit will be transmitted with security precautions. Data moving between application server and database or other data stores will be secured via Secure Socket Layer (SSL). Data from the PSFW+ application database will be transferred to Legacy's local servers via direct SSL connection with the database and stored on secure servers with restricted access rights. Data from the Vanilla Forums community software will be transferred to Legacy's local servers via SFTP ("Secure File Transfer Protocol" or "FTP over SSL"). Personally identifiable data (e.g. phone number, email address) associated with the PSFW+ application will be encrypted in the database.

Each subject will be assigned a unique, randomly-generated study identification number by clinic staff. This number will populate the key index field in the relational database structure. The MGUH and MMC ID Clinic research staff will maintain a secure database that links the study number with patient identifiers. For participants randomized to the PSFW+ condition, research staff will enter this study identification number into the website registration form which will be stored by Legacy. For those in the control condition, the identification will populate the back-end table of the Getting Healthy portal page. This will enable individual tracking of study participants and linking of website utilization metrics to other study data by StudyID. The Principal Investigators, research staff, and software development team will have access to individually identifying information about human subjects. Electronic data files with identifying information will be maintained securely and separately from other data files.

The ACASI questionnaire result uploads will contain the participant's unique study ID number, but no other personally identifying information. For these data the EISMU has implemented a comprehensive Security Program that conforms to the National Institute of Standards and Technology (NIST) standards and the EISMU official Certification and Accreditation documentation has been accepted by the NIH. The EISMU provides secure data hosting, access and backup services and data security provisions are applied systematically at multiple levels to ensure safe and accountable data storage and access. Multiple factor authentication is required for access to critical systems which include login and password authentication, individual token verification and IP address restrictions. The system complies with HIPAA requirements and utilizes a Secure Socket Layer certificate to ensure data encryption during data transmission. Servers maintain audit logs of all connections and data modifications with access to users granted after certification criteria are met. A fully virtualized environment, built on Dell's hardware and VMware's enterprise level hypervisor, is utilized to provide high performing and highly available systems. Advanced backup and

recovery systems are implemented to protect both complete server images and file level data. Redundancy is built into the infrastructure at various levels to minimize downtime in the event of an unexpected system failure including RAID disk arrays, bonded network interfaces, clustered VMware hosts, and file level replication. Cisco firewalls are used to protect all mission critical servers. Symantec Backup Exec and VMware Data Recovery are implemented as an enterprise backup/restore system. Critical database information is backed up at regular intervals to ensure minimal data loss in the event of a catastrophic disaster and to allow for both quick restoration of entire servers, as well as granular restoration of critical files. On site and off site backups include backups to disk (storage area network) and tape. A Virtual Private Network is available for remote access. The system employs a defense in depth model to safeguard data ensuring that only authorized users can access the network resources.

All personnel will receive certification in human subjects protections from the NIH Office of Human Subjects Research prior to beginning work on this project. Outside parties who may be afforded access include designees of the Institutional Review Board overseeing the study site and the National Institutes of Health and Department of AIDS.

Potential Risks

We anticipate four potential risks for participants in this study, though it is important to stress that the overall risk is judged to be low. **(1) Nicotine withdrawal symptoms:** Study participants who attempt to quit smoking will likely experience some withdrawal symptoms that may include anxiety, restlessness, anger, irritability, sadness, problems concentrating, appetite change and weight gain, insomnia, and decreased heart rate. There is no reason to believe that participation in this study would worsen nicotine withdrawal symptoms or that symptoms would differ based on randomization assignment. **(2) Breach in data-related confidentiality/privacy precautions or through self-disclosure of personal information in an online social network:** Breach in privacy or confidentiality may occur related to data collection, storage, or transit, or via personally identifiable information posted by study participants in the PSFW+ community. **(3) Emotional distress:** Participants may experience emotional distress consequent to the data collection process since assessment measures include questions about social support, loneliness, substance use, and psychiatric illness. Participants may also experience emotional distress subsequent to participation in an online community if conflicts should arise. **(4) Nicotine replacement therapy side effects:** More common side effects of the nicotine patch include local skin irritation at the site of the patch, nausea if the dose is too large or if the patient continues to smoke at a high level while using the patch, and disturbed and vivid dreams. Less common side effects include allergic skin reactions.

Alternative Treatments and Procedures

Alternatives to study participation include continuing to smoke and pursuing smoking cessation strategies outside of the study. Readily available and free cessation treatments will be described in the informed consent document.

5.B. ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent

PLWH smokers without contraindications to NRT will be referred by their primary care providers to the study staff who will be present in the clinic to screen and then enroll patients or schedule an enrollment visit. Primary care providers will be alerted to the study through provider staff meetings, study flyers, and presentations at Community Advisory Board meetings at both clinics. In the event we do not meet accrual goals, research staff will directly recruit patients in clinic waiting areas. MMC and MGUH both enjoy collegial academic relationships with nearby HIV-care centers caring for thousands of additional PLWH smokers, and these may serve as secondary referral sources if the need to augment recruitment arises. Study staff will screen referred patients to determine eligibility. Individuals who are not eligible for the study will receive the Positively Smoke Free smoking cessation brochure. Eligible patients will complete the informed consent process in a private room in or nearby the clinic. The informed consent document will describe the randomized trial, including the possibility of being assigned to either of the study conditions and the right to withdraw at any time. All aspects of the study, including the informed consent document and process, will be approved by the governing IRB prior to study recruitment. Subjects will be provided a copy of the completed informed consent document, the original will be placed in each subject's case report form, and a copy will be placed in a

dedicated section of each subject's medical record.

Protections Against Risk

(1) Nicotine withdrawal symptoms: All participants will be offered nicotine replacement therapy which is intended to reduce withdrawal symptoms. Worsening of depression and/or anxiety as a result of nicotine withdrawal is addressed in item 3 of this section.

(2) Risk of breach in confidentiality/privacy: All hard copy data will be stored in locked offices at MMC and MGUH ID Clinics. Computerized data will be protected by maintaining the data that links study number to high level identifiers (e.g. full name, medical record number) in a single, secure file at both clinic locations. Study computers will be password protected and secured behind the respective institutional firewalls. Data transit between the PSFW+ application server and database or other data stores will be secured via SSL. Data from the PSFW+ application database will be transferred to Legacy's local servers via direct SSL connection with the database and stored on secure servers with restricted access rights. Data from the Vanilla Forums community software will be transferred to Legacy's local servers via SFTP ("Secure File Transfer Protocol" or "FTP over SSL"). Data from the ACASI uploads, i.e. participants' questionnaire responses, will be transferred to the AECOM EISMU via secure Sharepoint connection. The system interoperates with email to distribute alerts and notifications, and audits all editing and updating of information on the site. In addition, the collaborative portals host and integrate with Citrix XenApp as an application delivery system which provides end-users with a fully encrypted session. Security arrangements for data maintained by the EISMU are detailed in the Protection of Study Data section above. If by any chance the security of the databases is compromised, study data will be numerically coded and useless to someone without a data dictionary. Prior to data transfer to the biostatistician for analysis, personally identifying information will be removed from data tables. The study staff will apply to the appropriate parties for a Certificate of Confidentiality to protect subjects supplying study data pertaining to illicit substance use and sexual preference. There are also privacy risks related to participating in an online social network. The study team has sought advice and counsel from HIV specialists, technology specialists, PLWH, and numerous lawyers before creating the PSFW+ Terms of Use and Privacy Policy. Registration on the site requires accepting the conditions spelled out in each of these documents which appear next to the "Submit" button on the registration page as well as in the header of all content pages. Both documents emphasize that anything a user posts in the community should be considered public information, and that others may assume that they have HIV/AIDS based on personal information they post on the website since it is a quit smoking website for smokers living with HIV.

(3) Emotional distress: Both ID Clinics offer on-site mental health support services and are situated in close proximity to their respective psychiatric emergency departments. Study subjects that indicate at any time in-person, on the phone, or in the community that they are experiencing distress (esp. worsening of depression and/or anxiety) will be advised how to avail themselves of appropriate emergency clinical services if the need should arise. In addition, subjects scoring out of range on the depression and/or anxiety indices included in the study questionnaires will be contacted by study staff and offered referral to mental health services. Drs. Shuter and Kumar will monitor and strictly adhere to adverse events reporting procedures within their clinics and IRBs. A data safety monitoring officer will oversee the data safety monitoring plan. Dr. Graham will conduct weekly supervision meetings with the PSFW+ Community Administrator, Ms. Jacobs, to discuss any issues that arise in the community that may be of concern. Ms. Jacobs will alert Dr. Graham immediately if a participant posts content in the community that indicates the potential for harm or adverse event. Dr. Graham will attempt to contact the participant using the phone number s/he provided during site registration to assess the potential for harm and refer to the emergency services protocol at each clinic. If the participant cannot be reached, Dr. Graham will contact hospital administration to activate the hospital's protocol for contacting patients about urgent matters when they are not reachable by phone. Each hospital will follow its respective protocol for calls to the patient's emergency contacts and/or dispatching police to locate the patient.

(4) Nicotine replacement therapy side effects: The risks of serious adverse effects of nicotine replacement therapy are small, and its potential health benefits far outweigh its risks. Subjects will be encouraged to review the drug information provided with the product and to report adverse effects to their clinic providers. Study candidates with contraindications to NRT or whose providers deem to be at unacceptable risk from NRT will be excluded from the study.

Adverse Event Response and Reporting

The MMC ID Clinic has primary care providers on-site Monday through Friday from 9am-5pm. During off hours, patients may contact covering attending physicians by pager 24/7/365 through an emergency beeper system. For emotional/psychological issues, the ID Clinic has an on-site mental health team consisting of two psychiatrists, a psychologist, and a social work therapist. During off-hours, the MMC psychiatric emergency department is located in an adjoining area of the hospital. The Georgetown Division of Infectious Diseases has an ID Fellow on call for emergency issues 24/7/365 who is able to reach Dr. Kumar. All study enrollees will be given the 24 hour number for the participant to call in the event of an urgent or emergent issue. Additionally the Division has access to the Department of Psychiatry with 24 hour coverage through the Emergency Department which is located in the MedStar Georgetown University Hospital on the University campus. For outpatient follow-up, the Department of Psychiatry utilizes psychiatrists, psychologists and licensed clinical social workers based on the needs of the subject.

5.C. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

Subjects may benefit from participation in this research in several ways. By participating in a smoking cessation treatment program, subjects may increase the likelihood that they will attempt to quit smoking and be successful. Additionally, participants will gain a greater understanding of their smoking behavior that may help them to quit successfully in the future. Finally, although this is not a direct benefit, all participants will be involved in a project to evaluate innovative treatments for smoking cessation in this highly vulnerable population that may ultimately produce an enormous public health impact. If proven effective, PSFW+ could be promoted at HIV care sites throughout the country as a broad-reach intervention that addresses an important health disparity. The belief that the benefits of smoking cessation interventions outweigh their risks is an accepted principle of medical practice. The only additional risks to study subjects in the proposed project are the risks of breach of patient privacy and emotional distress related to the data collection process. The investigators believe that these small risks are outweighed by the potential benefits of the study.

5.D. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Cigarette smoking continues to be a major preventable cause of death in the United States, and improvements in treatment options are needed specifically for PLWH. The scope of the problem of smoking in PLWH and the limits of knowledge related to smoking cessation in PLWH are highlighted in **Section 3.A.** The Internet has the potential to deliver a low-cost and effective cessation intervention to PLWH smokers throughout the US. Usage data and satisfaction survey responses may also be useful in planning future studies and optimizing future web interventions.

5.E. DATA AND SAFETY MONITORING PLAN

All aspects of the data safety monitoring plan will be reviewed and approved by the governing IRB prior to study initiation. Drs. Shuter and Stanton will be responsible for monitoring the safety and efficacy of this minimal risk study, executing the data and safety monitoring plan, and reporting the findings annually to the NIH. A Data Safety Monitoring Officer (DSMO) will be designated at Montefiore. S/he will be a physician without direct clinical responsibilities in the MMC ID Clinic, and without conflicts of interest relating to the proposed study. Parameters to be tracked, at least quarterly, will include subjects' sociodemographic characteristics, expected versus actual accrual statistics, study attrition, serious adverse events, and protocol amendments. The DSMO will receive a summary statement containing these data quarterly.

Mechanisms in place to protect patient privacy are detailed in **Section 5.B.** Additionally, study staff will apply to the appropriate authorities for a Certificate of Confidentiality to protect subjects supplying study data pertaining to illicit substance use and sexual orientation.

Serious adverse events (SAEs) will be defined as death, hospitalization, or immediately life-threatening illness (including mental illness). SAEs will be reported to the clinical site's IRB within 72 hours of study personnel becoming aware of them. The relationship of each SAE to study participation will be graded by the study staff as unrelated, probably not related, possibly related, probably related, or definitely related. Provisions for responding to psychiatric SAEs have been previously detailed (see **Section 5.B.**). For each SAE the DSMO, PI, and the IRB will consider whether the risk benefit ratio of the study has been altered necessitating study discontinuation, modification of the informed consent document, and/or notification of current study subjects. The site PI will notify the NIH of each SAE that occurs within 72 hours of awareness and will file a full SAE report for each event once clinical information becomes available.

5.F. REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

All members of the investigative staff have completed formal training programs in the protection of human research participants and will maintain current certification throughout the course of the trial. Documentation of program completion will be supplied to the NIH prior to project initiation.

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Amendment for *Randomized Controlled Trial of An Internet Cessation Program Plus Online Social Network for HIV + Smokers* (IRB# 2015-4723)

Amendment Date: 10-4-21

Overview of the proposed amendment

This amendment is being submitted to expand the scope of the previously approved study. The specific changes sought by this amendment include:

1) Inviting participants previously enrolled in the parent study to participate in a new telephone survey.

2) Inviting those participants reporting abstinence from cigarette smoking during the telephone survey to participate in an in-person study visit to measure exhaled carbon monoxide and undergo a cheek swab for biobanking.

Background for the amendment

The parent study of this amendment, a *Randomized Controlled Trial of An Internet Cessation Program Plus Online Social Network for HIV + Smokers,* was closed in 2020 and represents the first randomized controlled trial of tobacco treatment to report abstinence efficacy at the 6-month timepoint among people with HIV (PWH) smoker in the US[1]. This well characterized cohort of study participants represents an important population for understanding predictors of long-term smoking cessation. Additionally, this population represents an opportunity to elucidate associations between smoking cessation and healthcare utilization, outcomes related the COVID-19 and vaccination for COVID-19, and HIV care.

Ref:

[1]Stanton CA GA, Kim RS, Chander G, Shuter J. Multicenter RCT of a web-based cessation program plus online social network for HIV+ smokers. Presented at the Society for Research on Nicotine & Tobacco 2021 annual meeting, Feb. 24-27, 2021.

Objectives

The objectives of the study proposed in the amendment are to:

1. Describe rates of and duration of tobacco abstinence, and identify clinical and demographic factors associated with maintenance of abstinence, among participants of the parent study.

2. Identify associations between smoking status and COVID-19 related outcomes and healthcare utilization among participants of the parent study.

3. Identify associations between smoking status on HIV-related outcomes and healthcare utilization among participants of the parent study.

Methods

This will be a prospective study of participants in the trial: *Randomized Controlled Trial of An Internet Cessation Program Plus Online Social Network for HIV + Smokers.* The trial was conducted at two sites, Montefiore Medical Center and Johns Hopkins University Hospital. Only the participants from the Montefiore site will be invited to join the follow-up study proposed in this amendment. For the sake of the amendment, "participants" refers to participants at Montefiore. All prior participants in the study are eligible for this proposed follow-up study. Study personnel will contact prior participants via telephone to offer participation in the follow-up study.

The first component of the follow-up study will include a 15-20 minute IRB-approved telephone interview with questions related to: current smoking status; smoking quit attempts; motivation to quit; alcohol and drug use; COVID-19 illness, management, vaccination status, and attitudes toward vaccination; overall healthcare utilization over the prior year including visits with an HIV provider, emergency department visits, and hospitalizations; and questions related to perceptions of HIV care.

Participants who report tobacco abstinence during the telephone interview will be invited for an in-person visit to measure exhaled carbon monoxide and to submit a cheek swab for biobanking for future genetic research. Both of these are painless, essentially risk-free procedures.

Data Security:

Data will be collected and stored using a secure, password protected database accessible only to authorized study personnel. Data will be de-identified and all participants will be assigned a unique identifier. A file linking identifying information to unique identifiers will be kept separately from the data itself and will be stored in a locked file cabinet within a locked office, only accessible to authorized study personnel. Upon completion of the analysis, the documents linking the identifiable data to unique study identifiers will be destroyed.

Data Analysis:

Participants achieving tobacco abstinence will be compared to those not achieving abstinence according to clinical characteristics, sociodemographic characteristics, and interview responses. Using standard bivariate and multivariate methods, we will identify factors associated with tobacco abstinence, healthcare utilization, COVID-19 related outcomes and interview responses, and HIV-related outcomes and interview responses.

Informed Consent

All participants will undergo the process of informed consent prior to enrollment in this follow- up study. For participants in the telephone interview component, verbal informed consent using an IRB-approved script will be obtained. For participants in the in-person visit component, signed informed consent using an IRB-approved document will be obtained. Participants agreeing to the cheek swab for biobanking of genetic material for future research will also provide signed informed consent for that specific procedure.

Reimbursement:

Participants who consent to and complete the telephone interview will be reimbursed $20 for their time. Participants completing the in-person study visit will be reimbursed and additional $50. Participants participating in the in-person study visit will also be reimbursed for with a $6 Metrocard for roundtrip travel to the study site.

Risks/Benefits/Alternatives:

For participants of the telephone interview and in-person study visit, the primary risk will be loss of confidentiality. This risk is mitigated by the data security procedures described above. Participants may also feel uncomfortable with certain questions. If this occurs, participants can choose to end their participation at any time. For participants of the in-person study visit, the measurement of exhaled carbon monoxide is non-invasive and the cheek swab is minimally invasive, both with virtually no risk. Participants may choose to end their participation at any time during the study.